

D

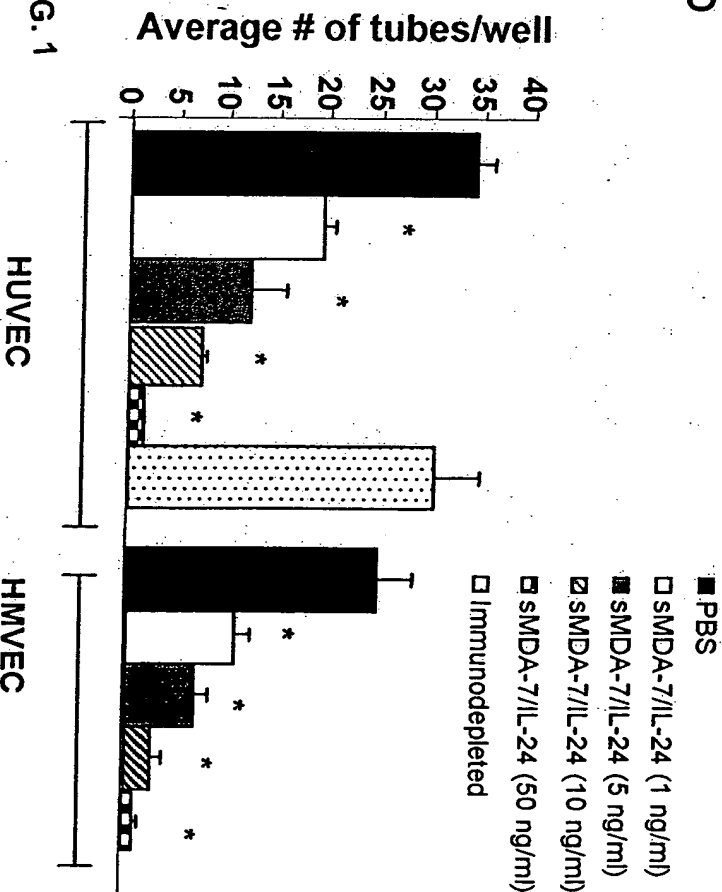


FIG. 1

HUVEC

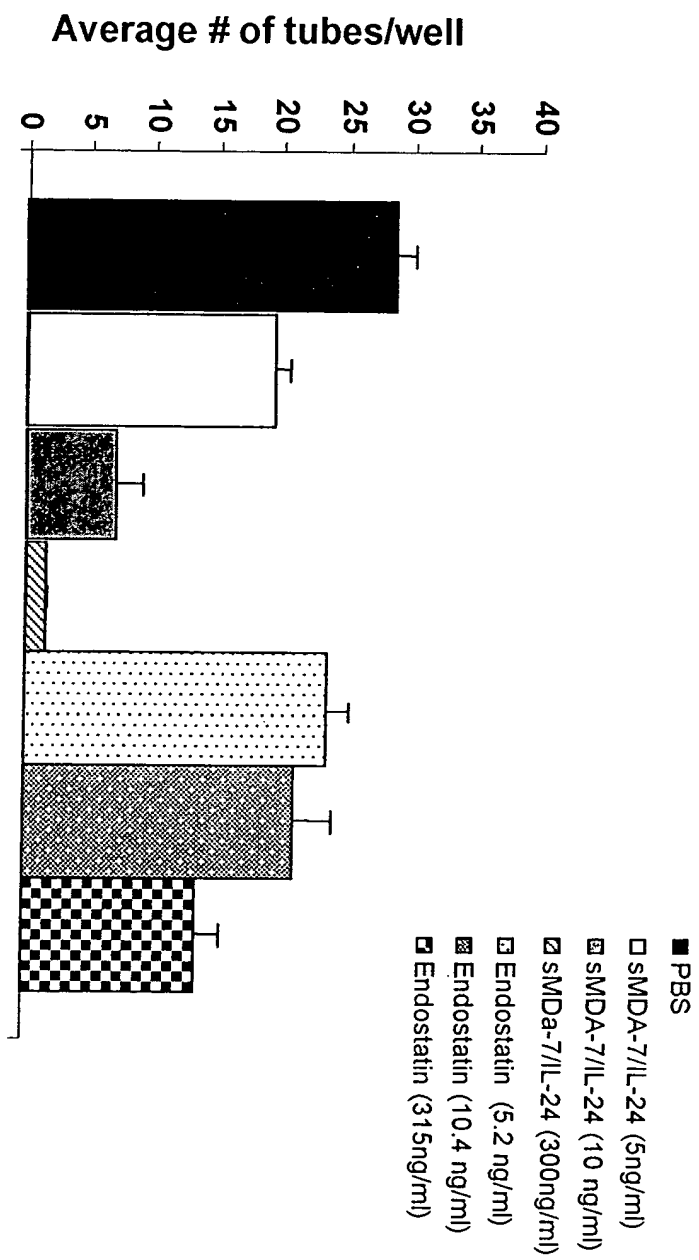


FIG. 2

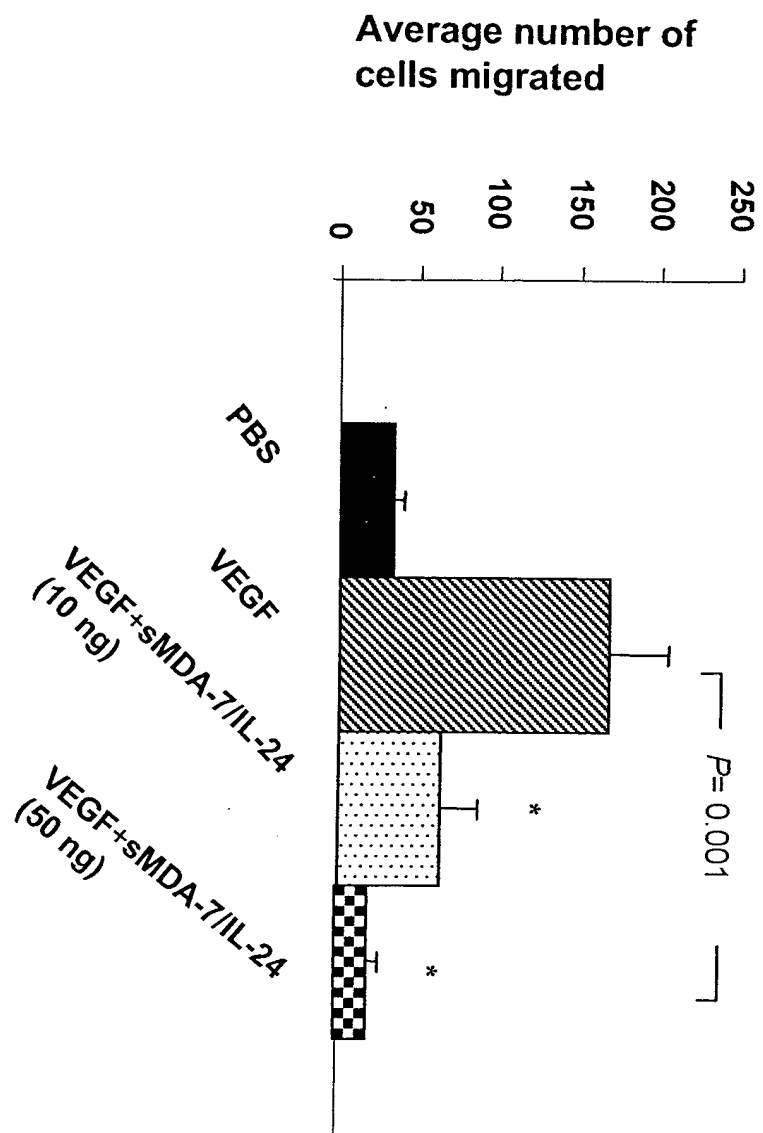


FIG. 3

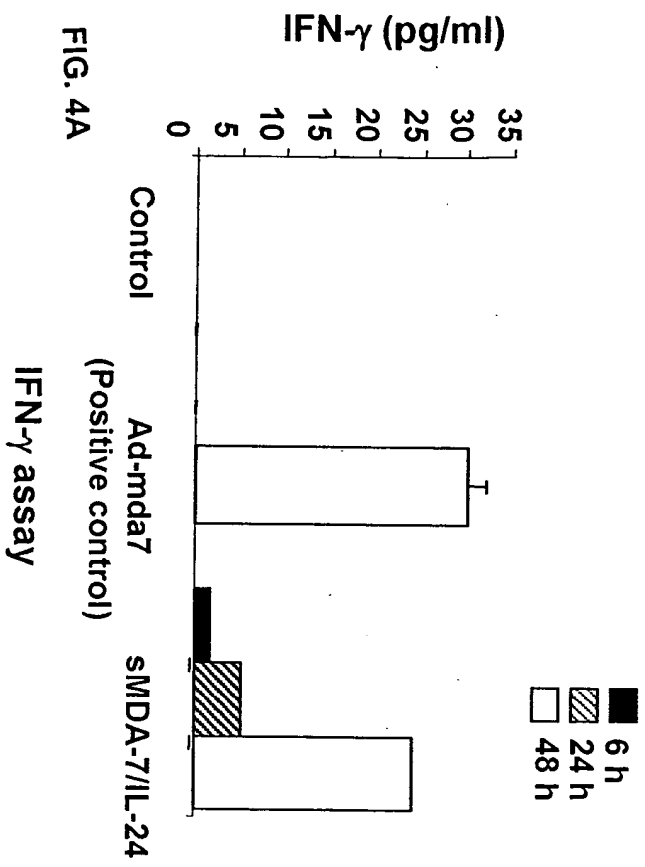


FIG. 4A

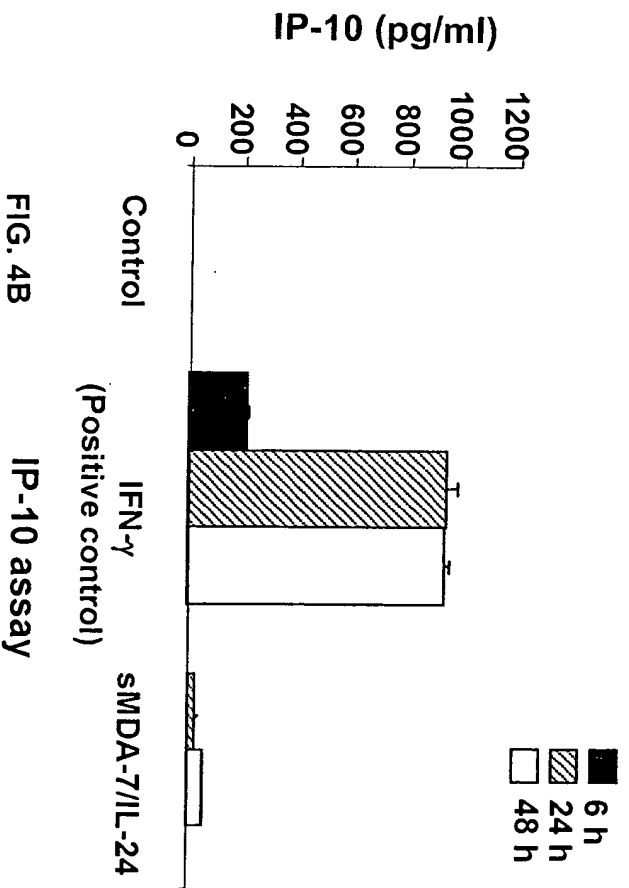


FIG. 4B

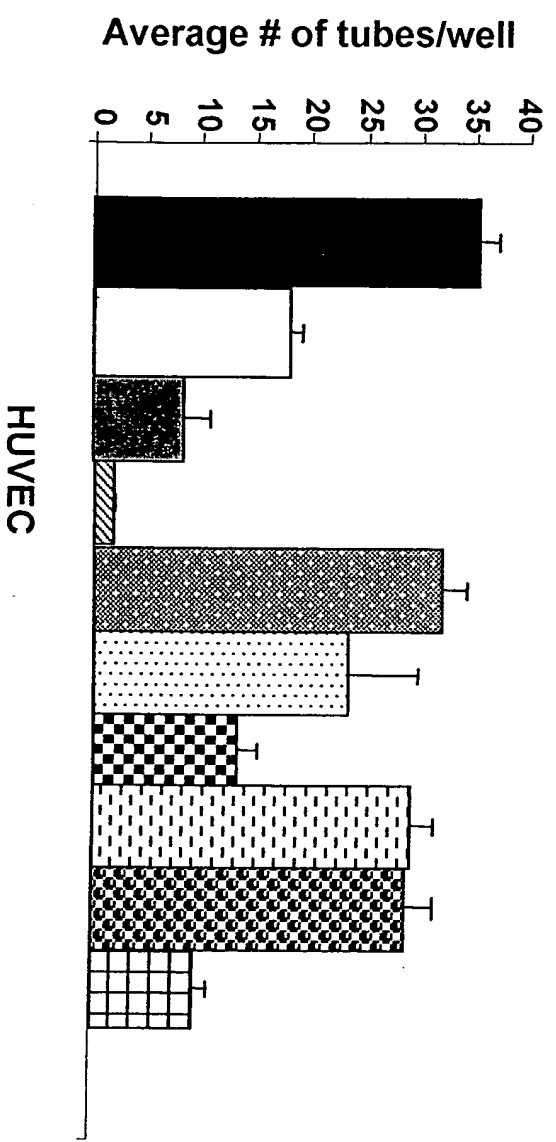
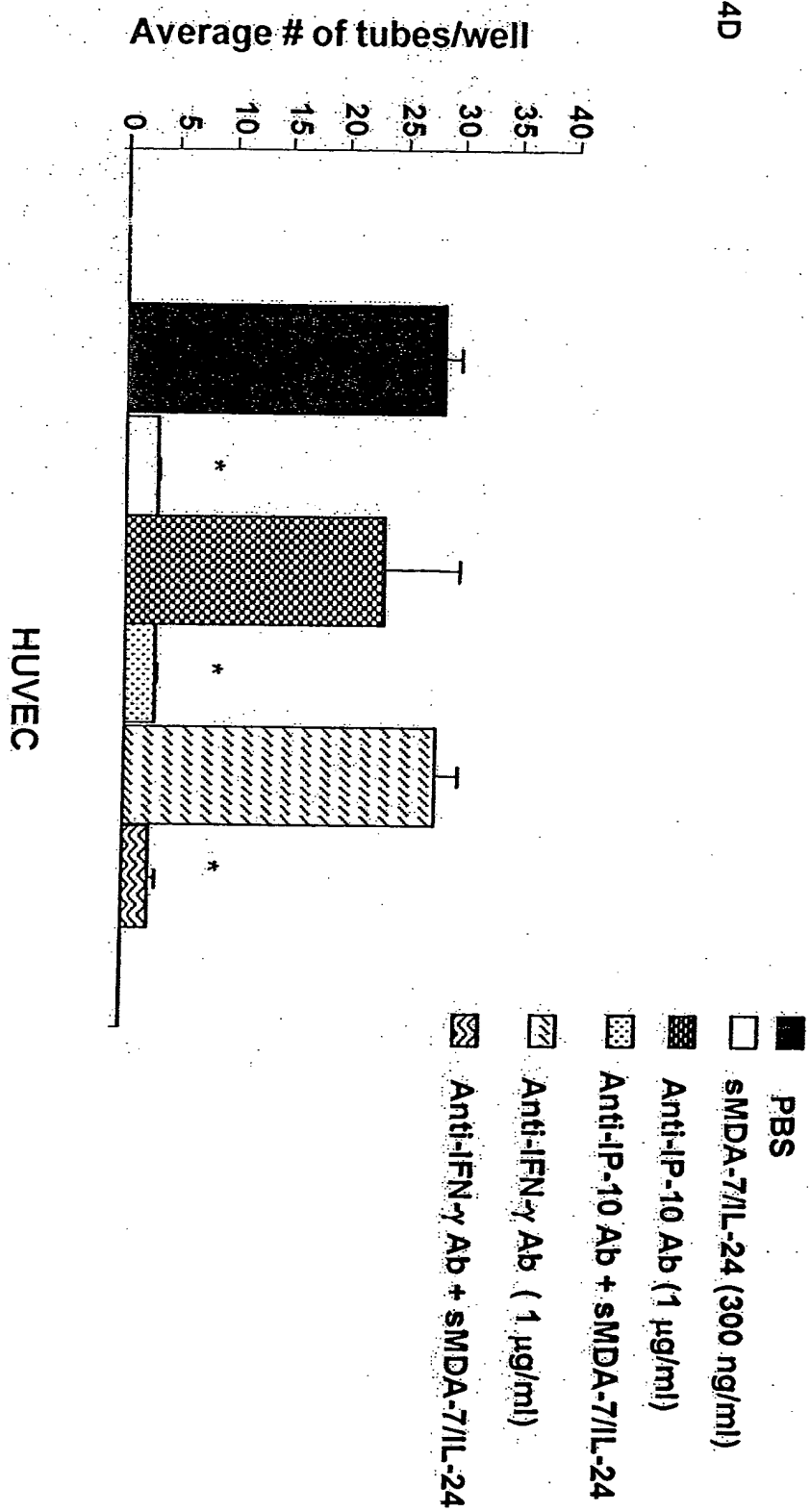


FIG. 4C

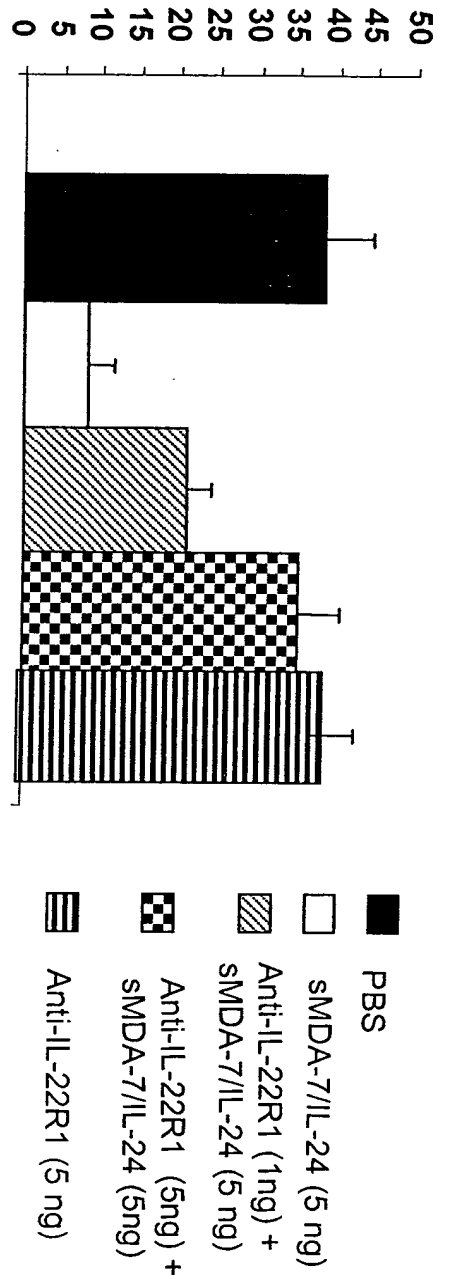
- PBS
- sMDA-7/IL-24 (5ng/ml)
- ▨ sMDA-7/IL-24 (10 ng/ml)
- ▩ sMDA-7/IL-24 (300 ng/ml)
- ▧ IFN- γ (4.5 ng/ml)
- ▦ IFN- γ (9 ng/ml)
- ▤ IFN- γ (268 ng/ml)
- ▣ IFN- γ (2.4 ng/ml)
- ▢ IFN- γ (4.5 ng/ml)
- ▧ IP-10 (134 ng/ml)

FIG. 4D



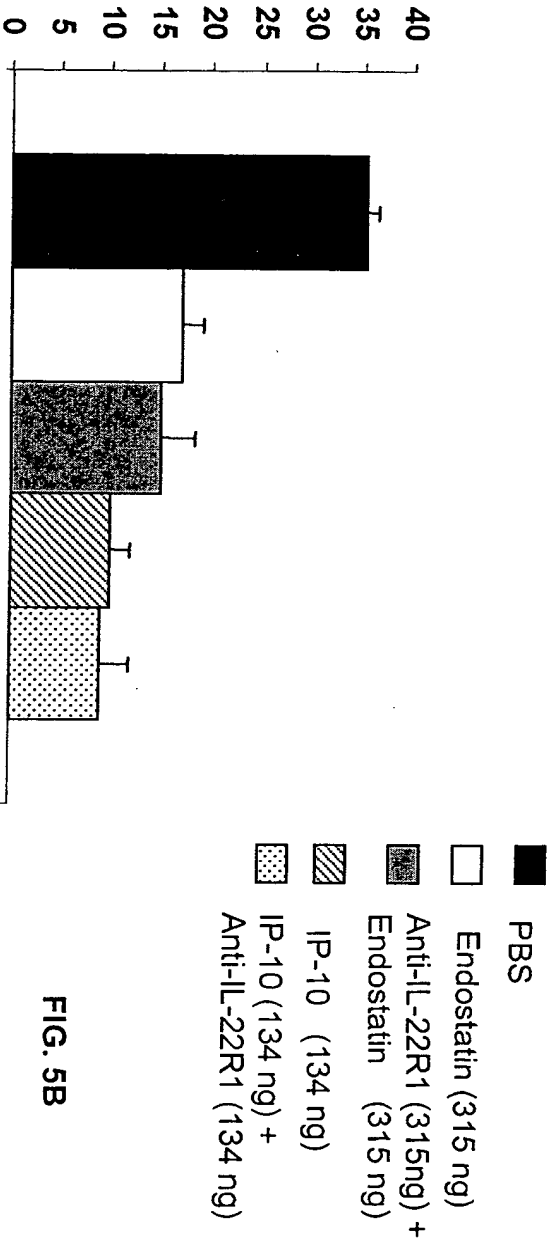
Average # of tubes/well

FIG. 5A



Average # of tubes/well

FIG. 5B



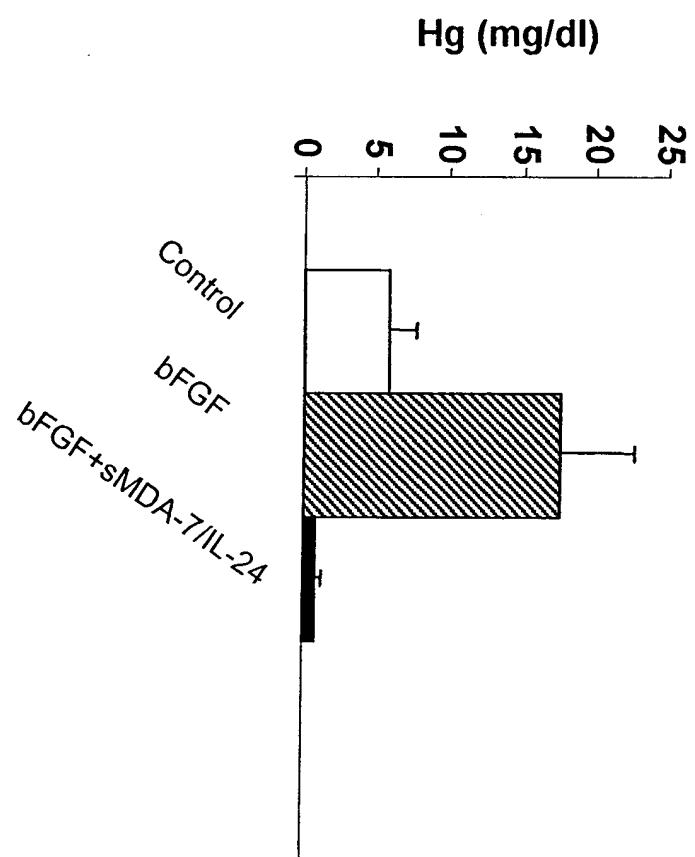


FIG. 6A

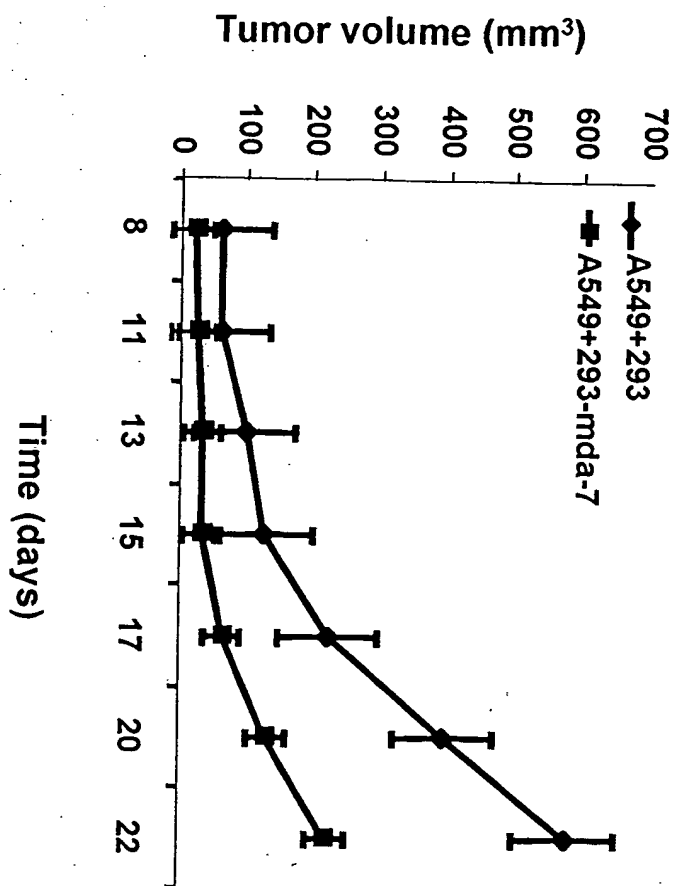


FIG. 6B

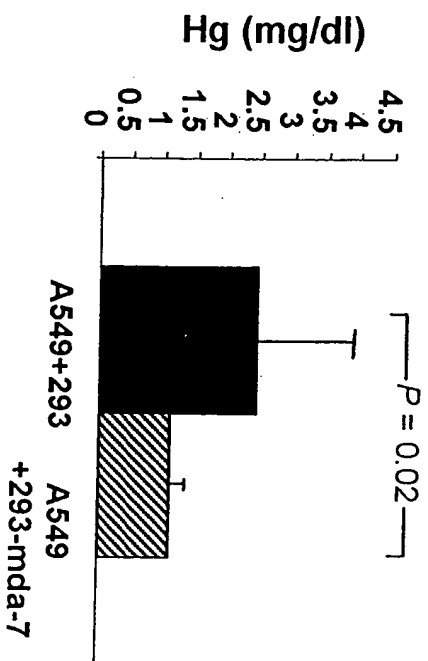


FIG. 6C

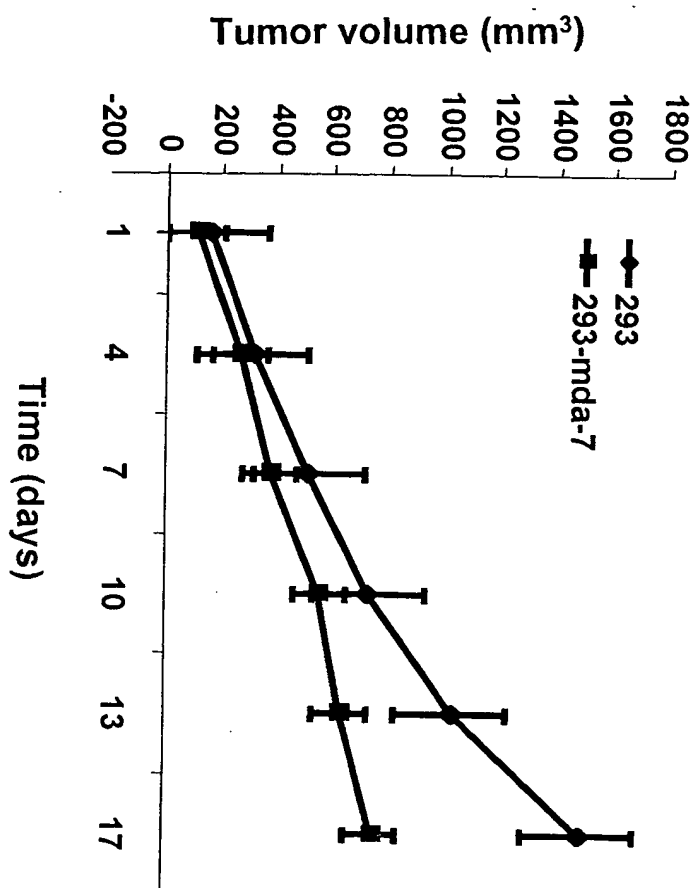
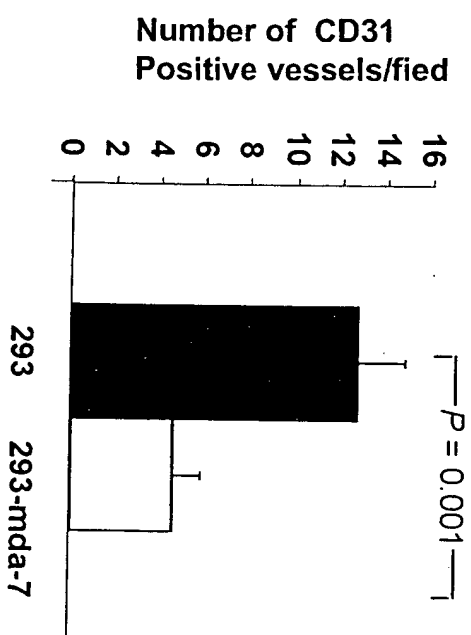


FIG. 6D

FIG. 6E

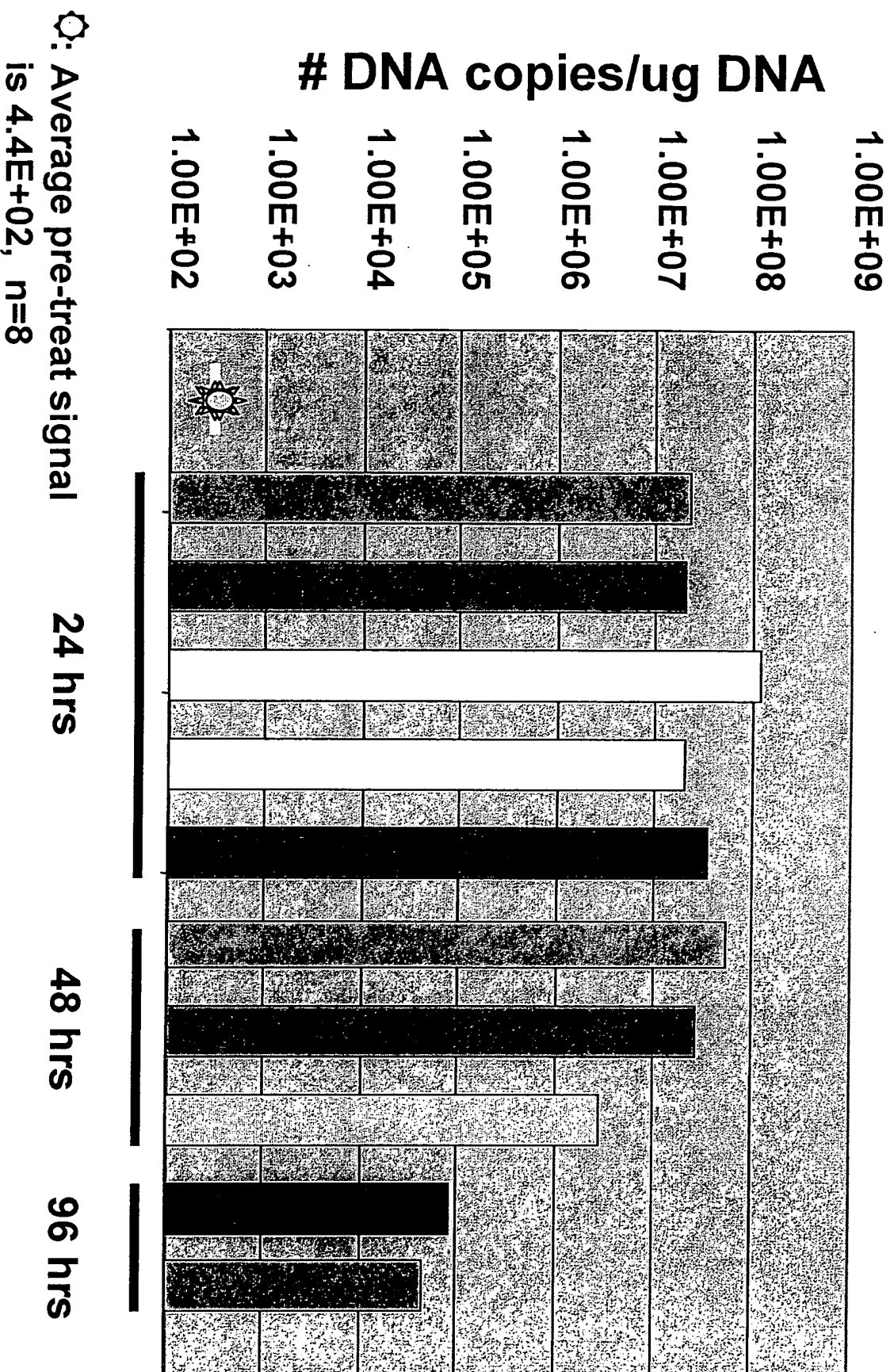


Study design

FIG. 7

Cohort #	# of patients	Viral dose (particles)	biopsy time (post inj.)
1	1	2x10 ¹⁰	24 hrs
2	1	2x10 ¹¹	24 hrs
3	3	2x10 ¹²	24 hrs
4	3	2x10 ¹²	48 hrs
5	3	2x10 ¹²	72/96 hrs
6	3	2x10 ¹² (divided doses)	48 hrs
7	5	2x10 ¹²	Core bx @30 days
8	5	2x10 ¹² (2x/wk x 3 wks)	Core bx @ 30 days

FIG. 8



(Pre-treat MDA-7 IHC – all negative)

<u>Pt</u>	<u>Time (hr)</u>	<u>MDA-7 ctr</u>	<u>MDA-7 periph</u>	<u>TUNEL ctr</u>	<u>TUNEL periph</u>
1	24	20%	0%	20%	0%
2	24	30%	5%	70%	10%
3	24	75%	40%	50%	30%
4	24	35%	5%	n.d.	n.d.
5	24	50%	25%	25%	17%
6	48	>60%	20%	40%	17%
7	48	60%	5%	70%	10%
8	48	20%	0%	5%	0%
9	96	50%	25%	80%	25%
10	96	90%	0%	35%	0%

FIG. 9

MDA-7/ TUNEL correlation $p < 0.01$

Kinetics of Serum Cytokine Response to INGN 241

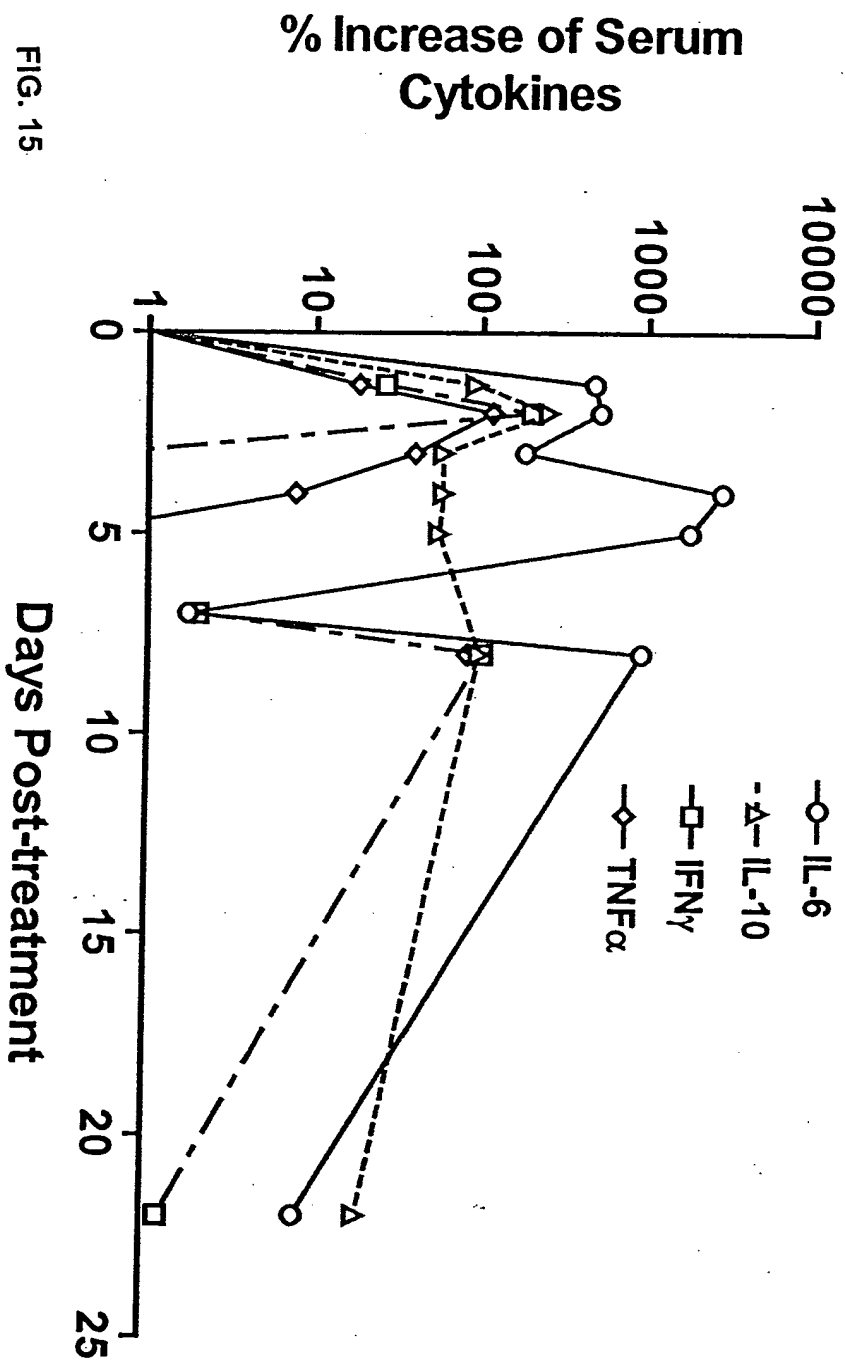


FIG. 15

FIG. 10

Serum Cytokine Response to Intratumoral INGN 241 Treatment.

<u>Cohort</u> (dose)	<u>No. pts</u> <u>tested</u>	<u>No. positive (mean % peak increase)</u>				
		<u>IL-6</u>	<u>IL-10</u>	<u>IFNγ</u>	<u>TNFα</u>	<u>GM-CSF</u>
1 (2x10 ¹⁰)	1	1 (298%)	1 (291%)	1 (>1,000%)	0	1 (150%)
2 (2x10 ¹¹)	1	1 (143%)	1 (599%)	1 (281%)	1 (864%)	0
3 (2x10 ¹²)	3	1 (>1,000%)	1 (134%)	1 (317%)	2 (345%)	1 (100%)
4 (2x10 ¹²)	3	3 (>1,000%)	3 (221%)	1 (173%)	2 (71%)	1 (120%)
5 (2x10 ¹²)	3	3 (640%)	3 (400%)	1 (317%)	2 (156%)	0
7 (2x10 ¹²)	7	5 (604%)	6 (387%)	3 (860%)	3 (255%)	0
Total	18	14	15	8	10	3

FIG. 11

Level of Increased CD8+ T cell Frequency in Pts who Received Intratumoral INGN 241.

<u>Cohort</u> (dose)	<u>No. pts</u> <u>tested</u>	<u>No. with</u> <u>increased</u> <u>CD8+ T cells</u>	<u>Mean % CD3+CD8+ T cells¹</u>		
			<u>Pre-</u> <u>treatment</u>	<u>Post-</u> <u>treatment @</u>	<u>Day</u> <u>Post-treat.</u>
1 (2x10 ¹⁰)	1	0	29 %	27%	
2 (2x10 ¹¹)	1	1	32 %	44%	Day 15
3 (2x10 ¹²)	3	3	33%	59%	Day 15
4 (2x10 ¹²)	3	1	35%	44%	Day 30
5 (2x10 ¹²)	3	1	22%	29%	Day 15
7 (2x10 ¹²)	7	2	30%	40%	Days 15-30
Total	18	8	31%	44%	Day 15

FIG. 12

Increase in Peripheral Blood CD8+ T Cells Following intratumoral INGN 241 Injection

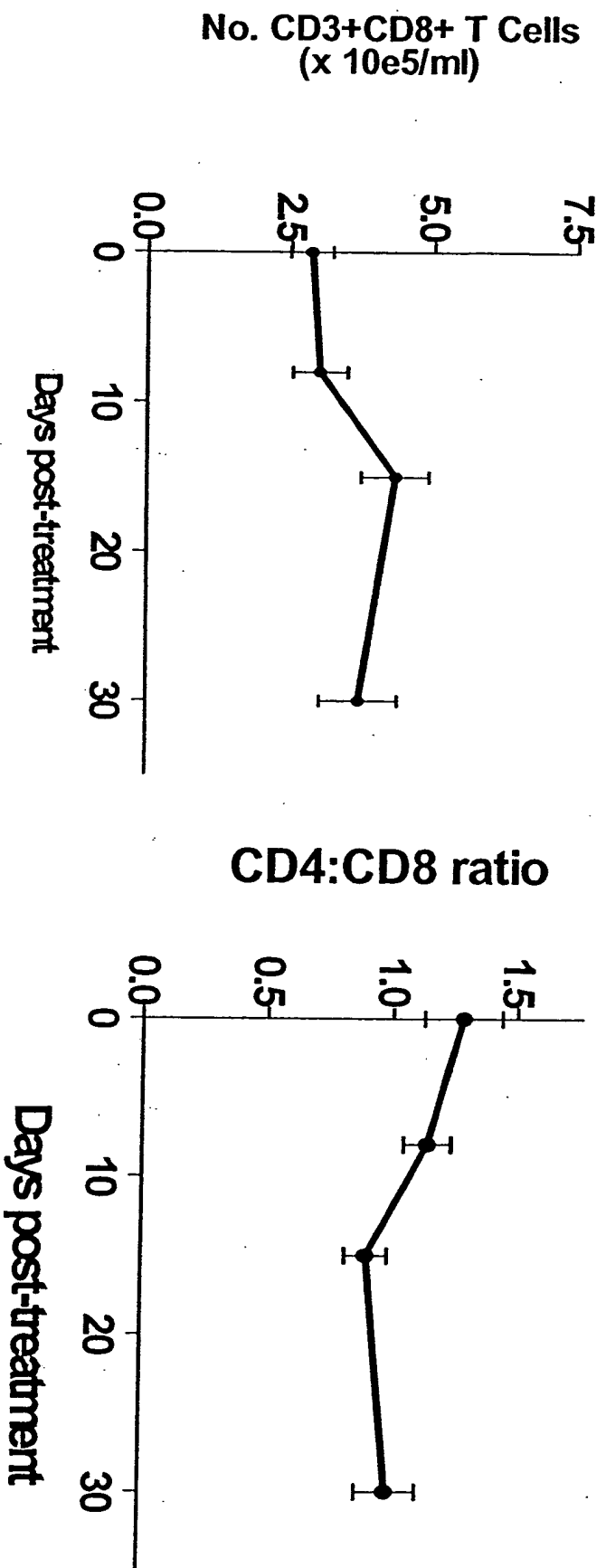


FIG. 13

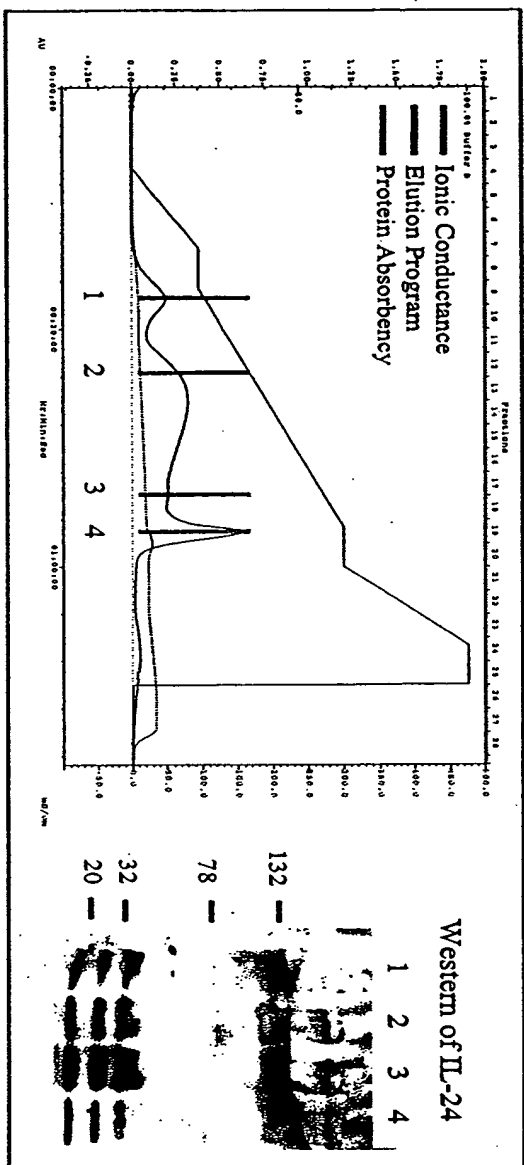


FIG. 14

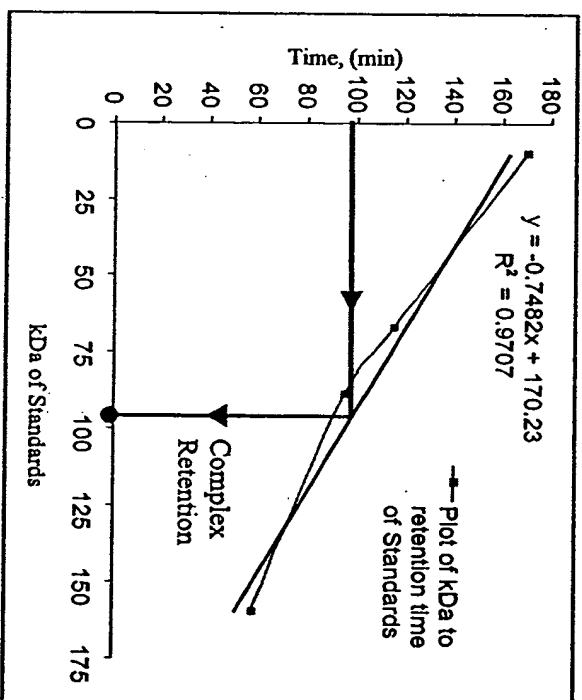


FIG. 15

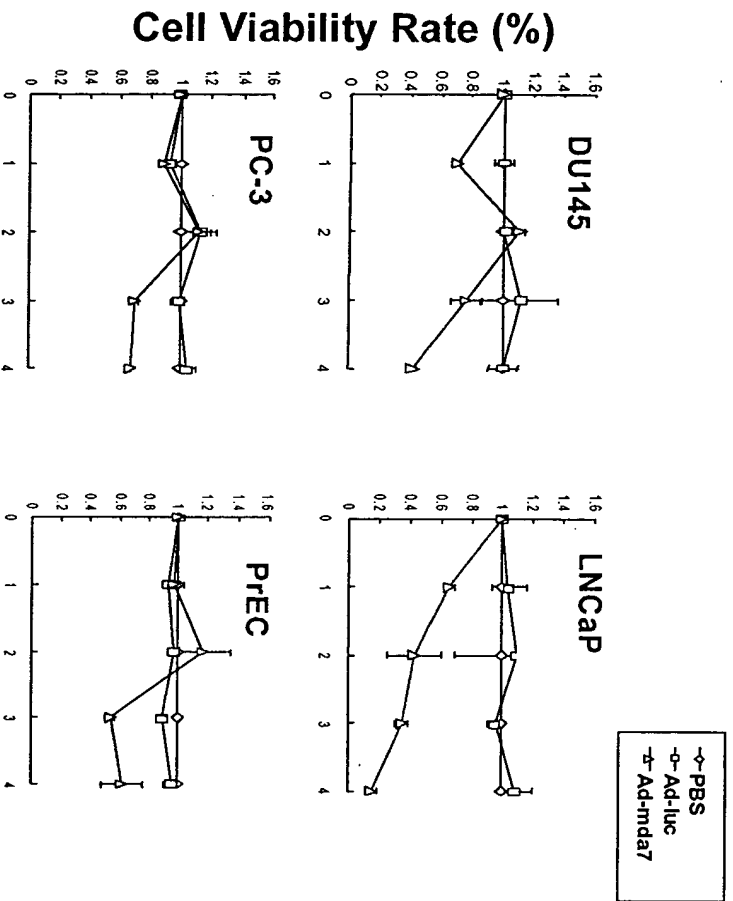


FIG. 16

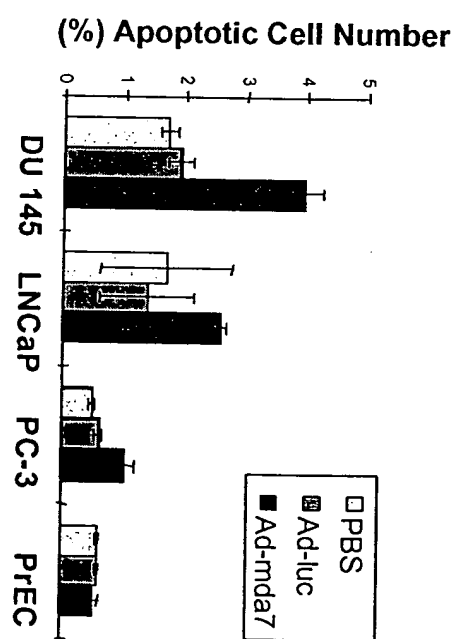
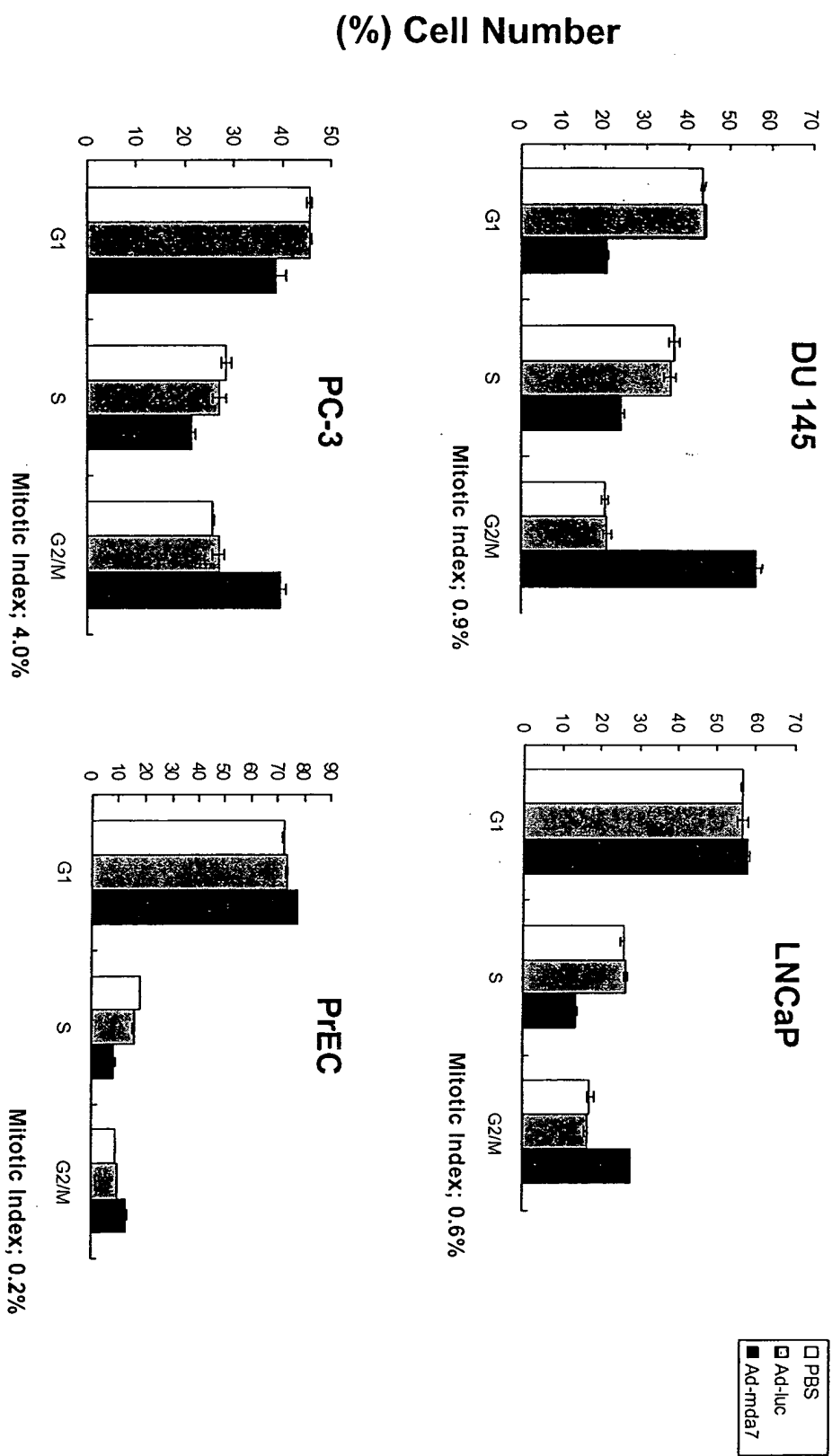


FIG. 17



Cell Cycle Phase

FIG. 18

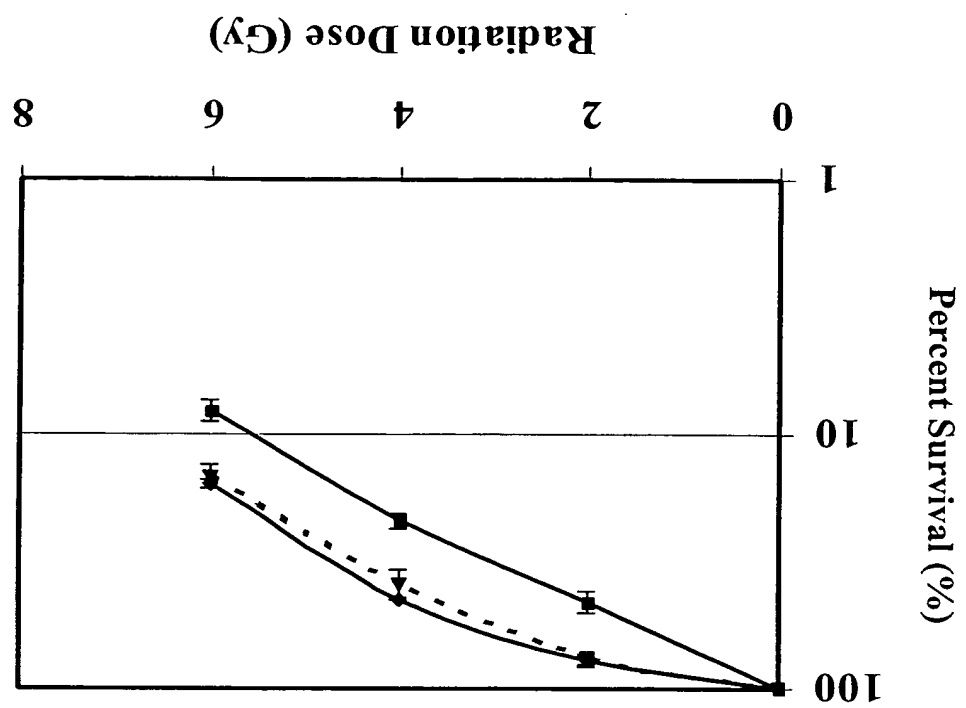


FIG. 19A

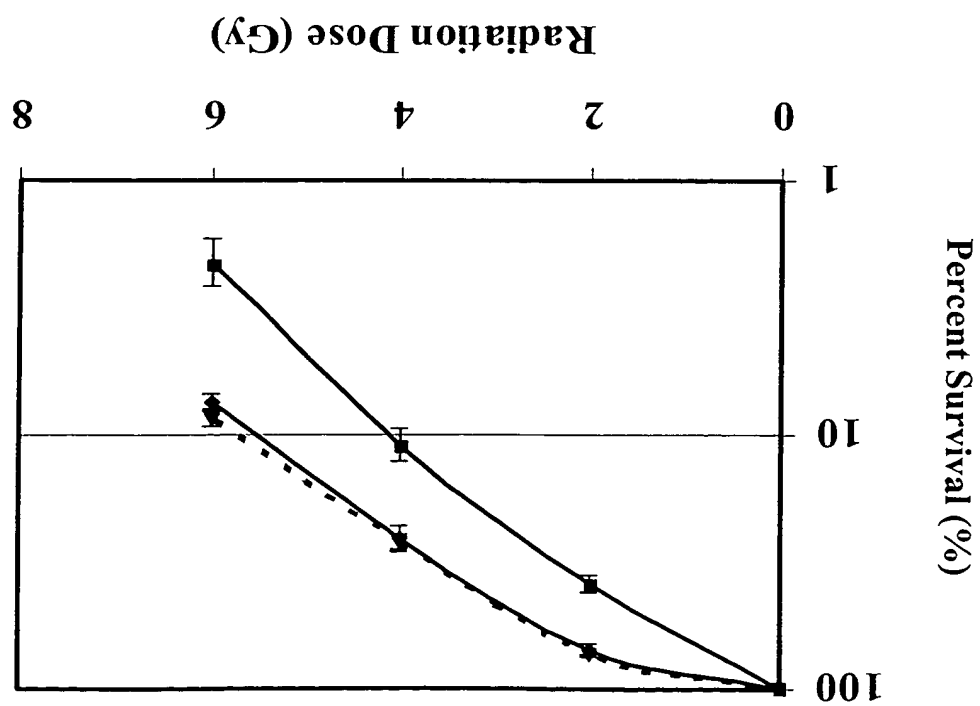


FIG. 19B

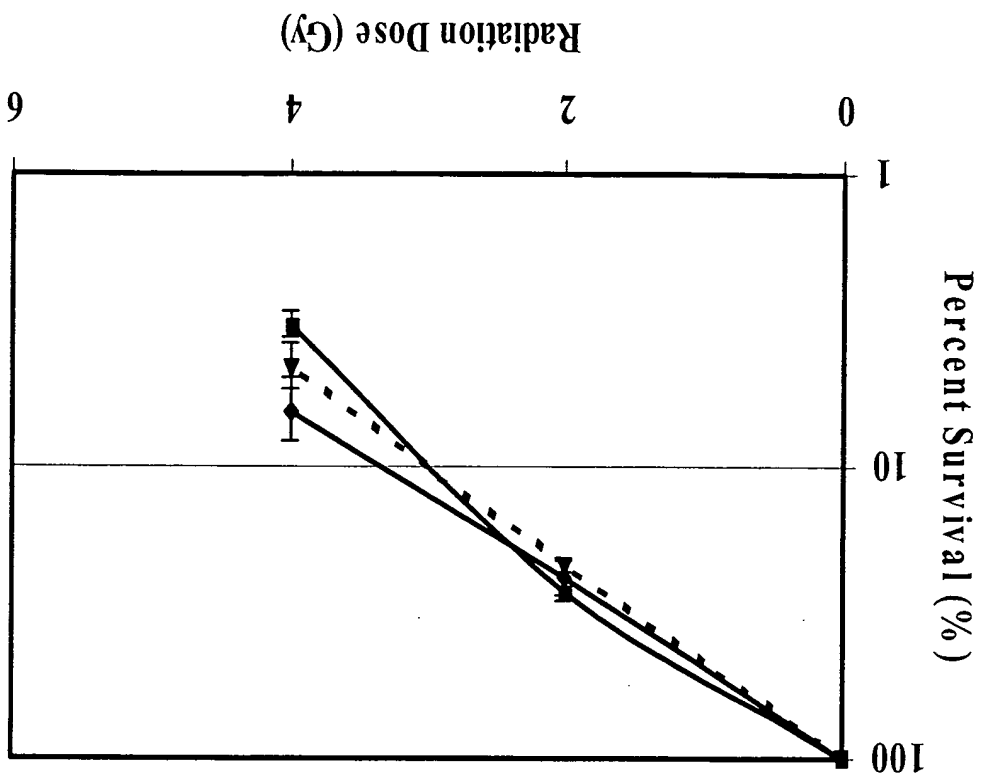


FIG. 19C

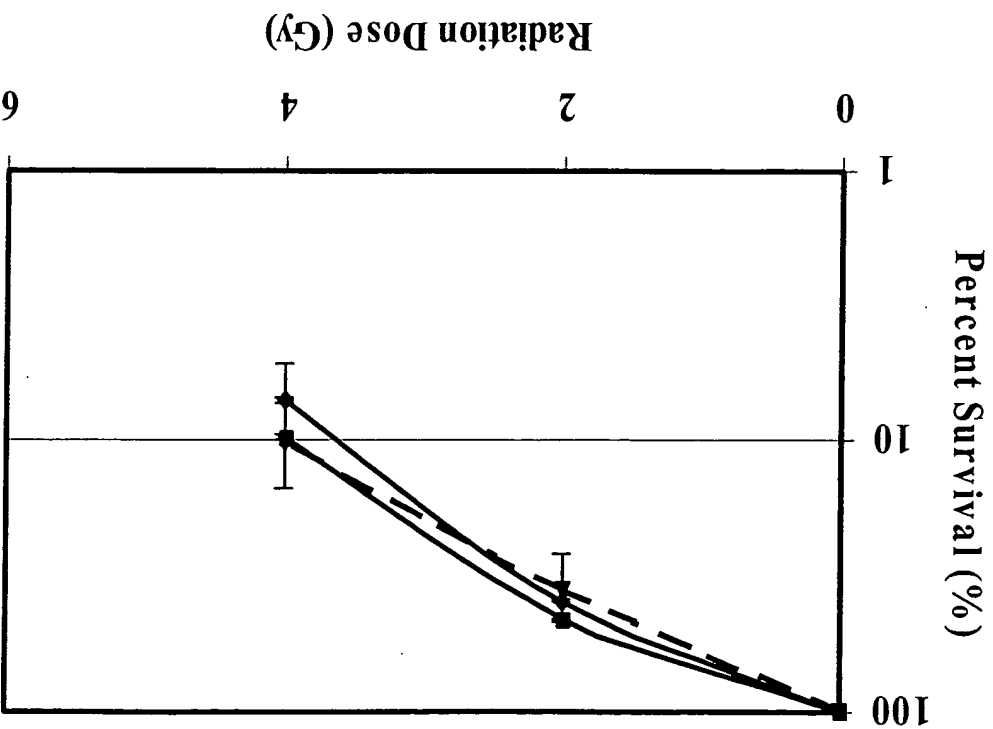
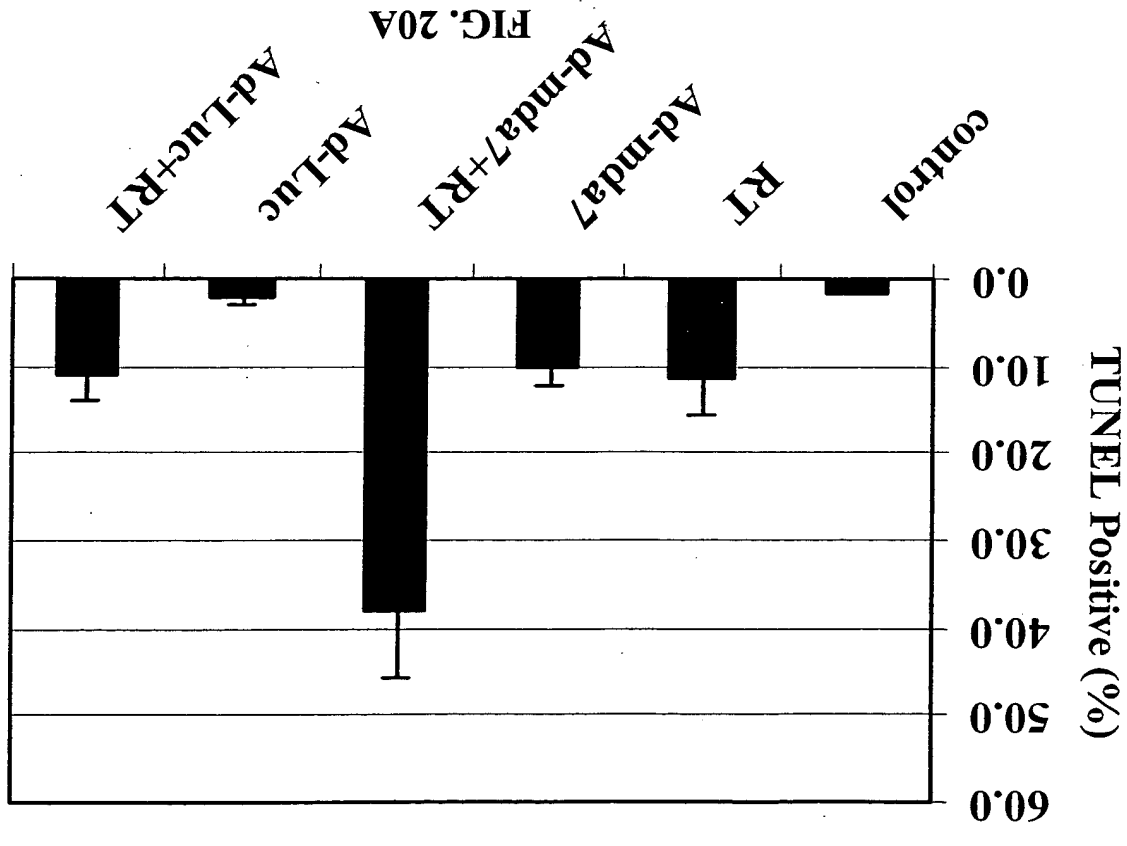
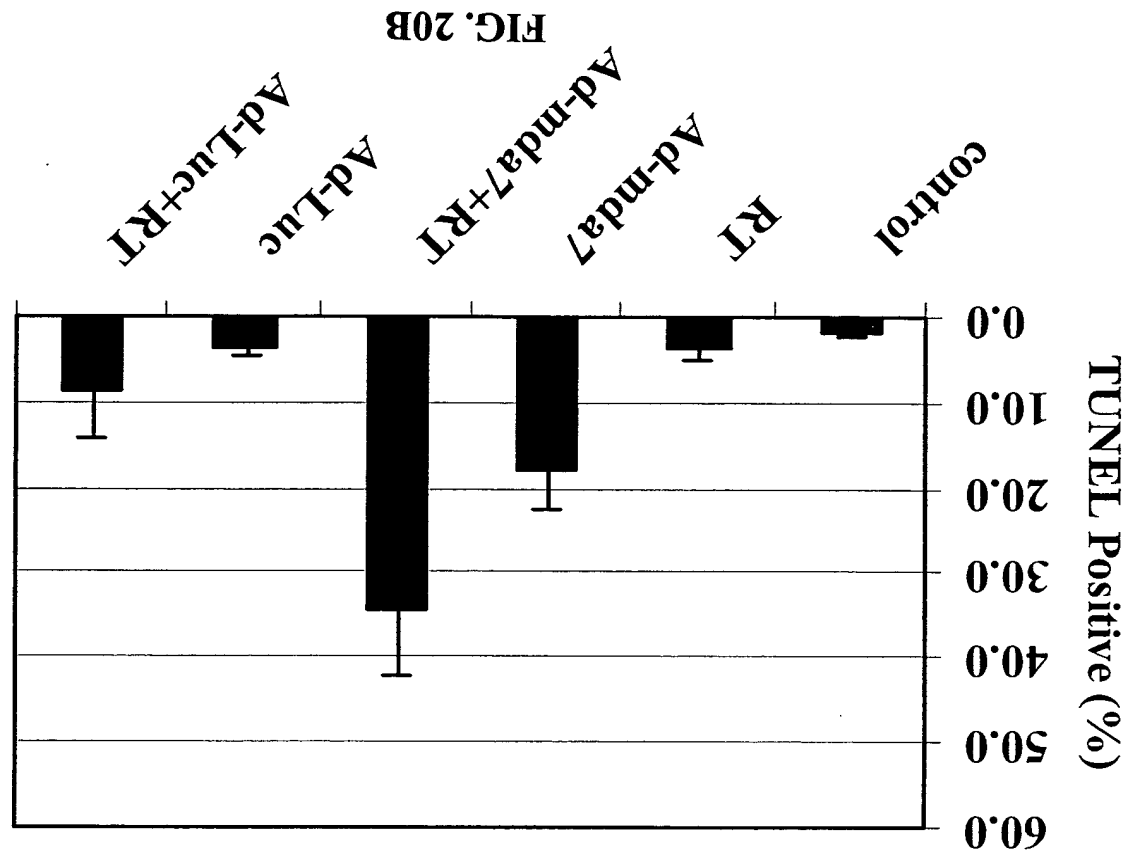


FIG. 19D



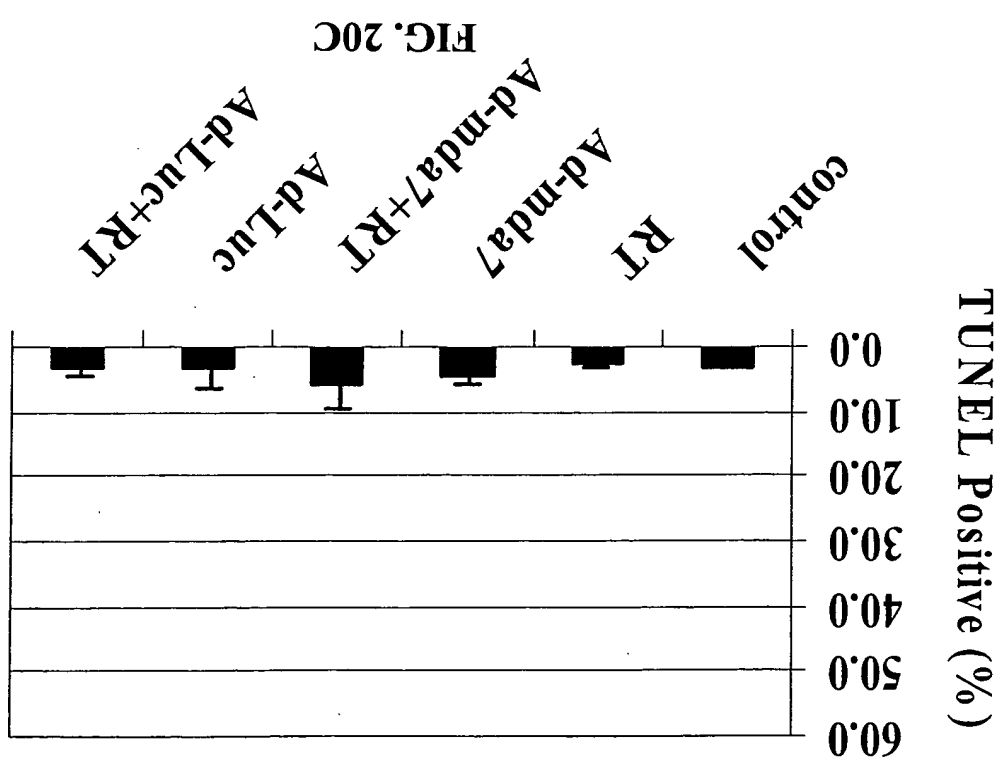
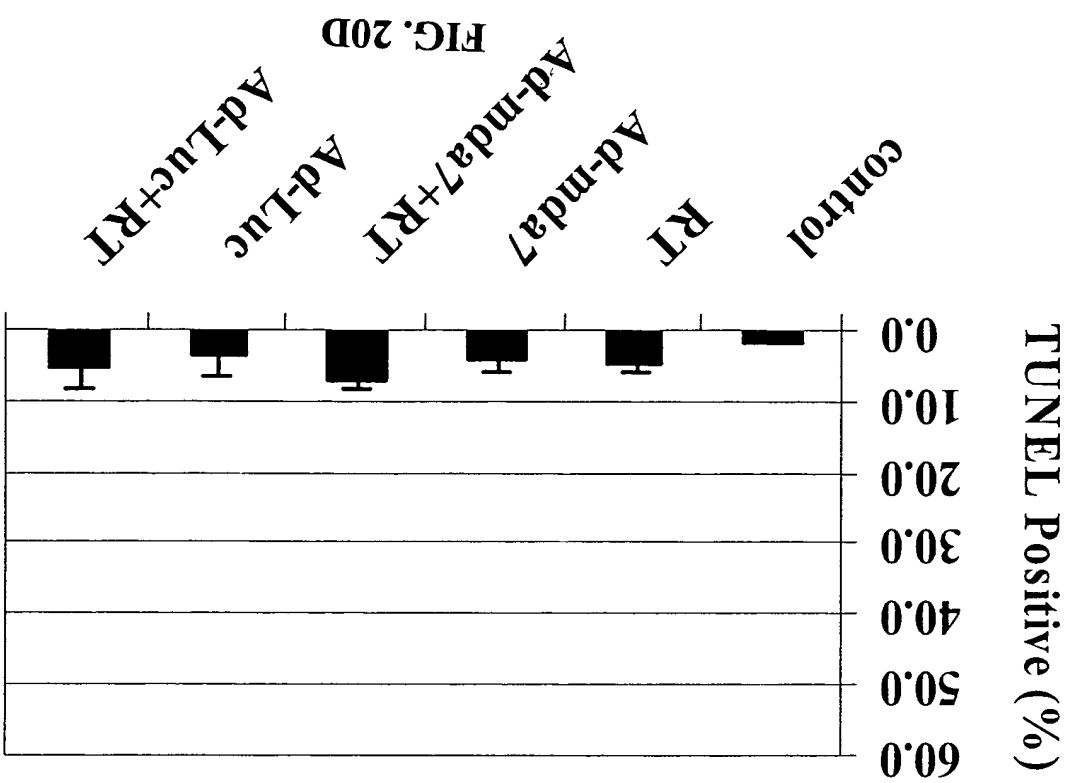


FIG. 21

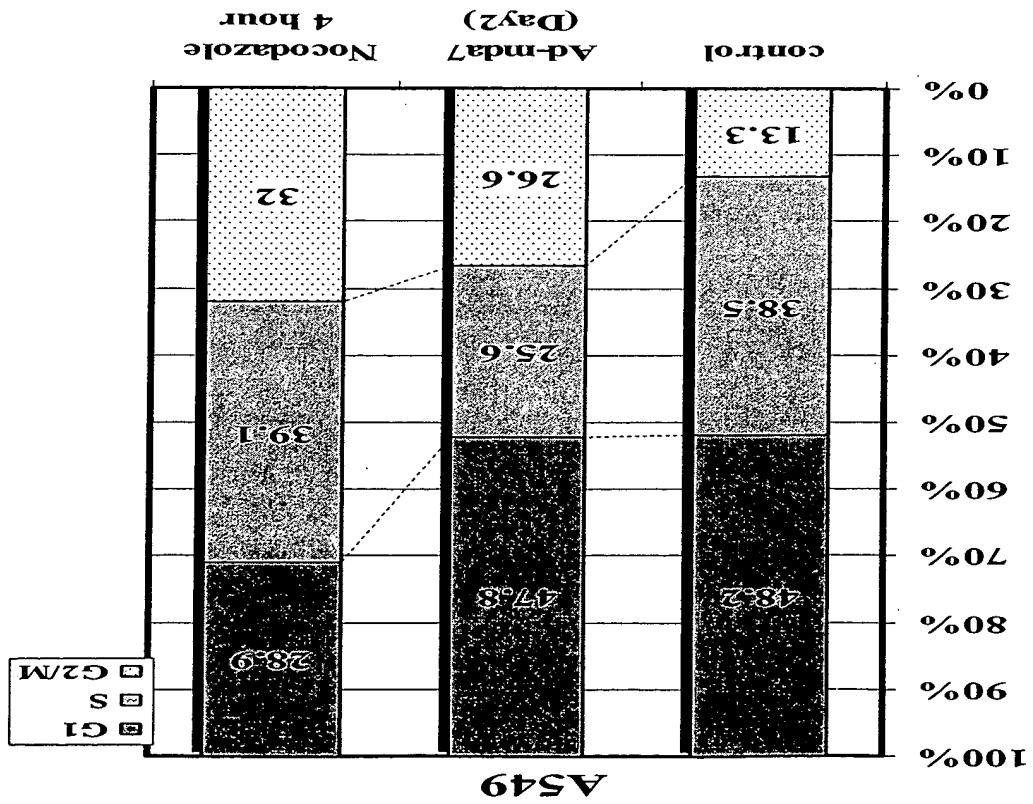
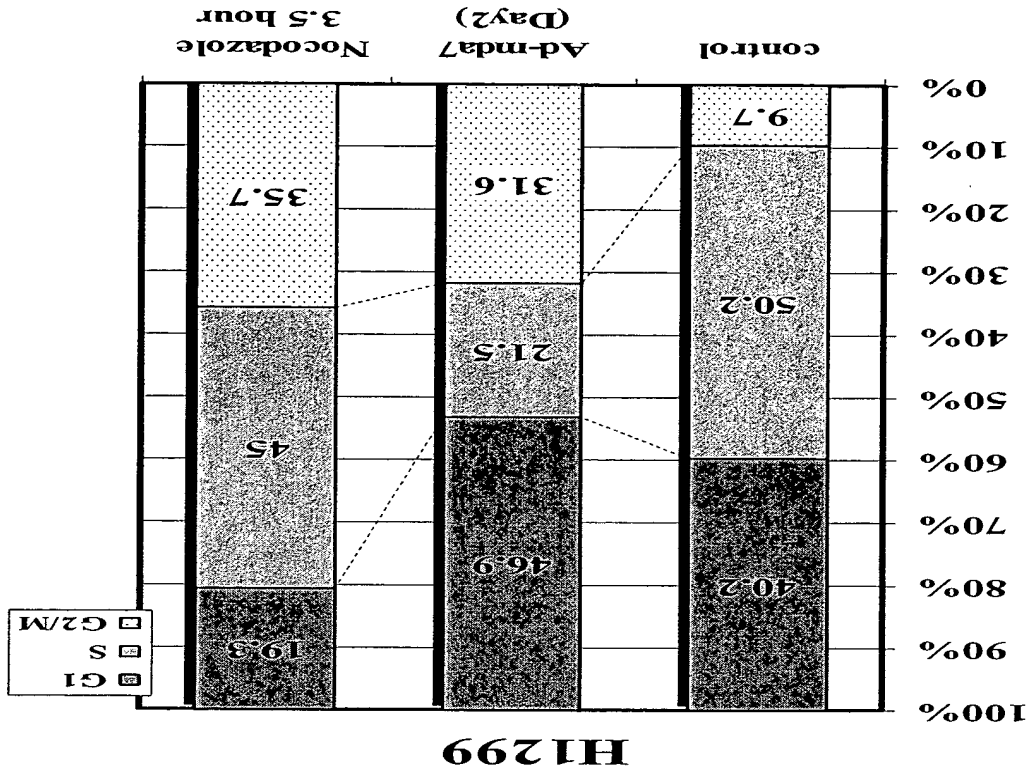


FIG. 22

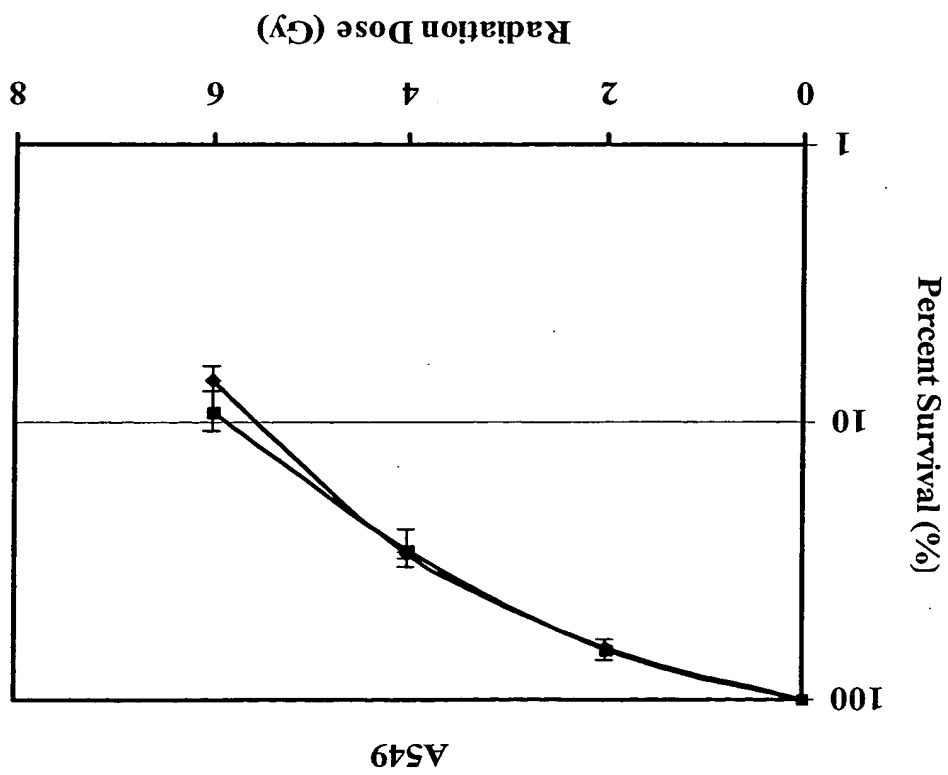
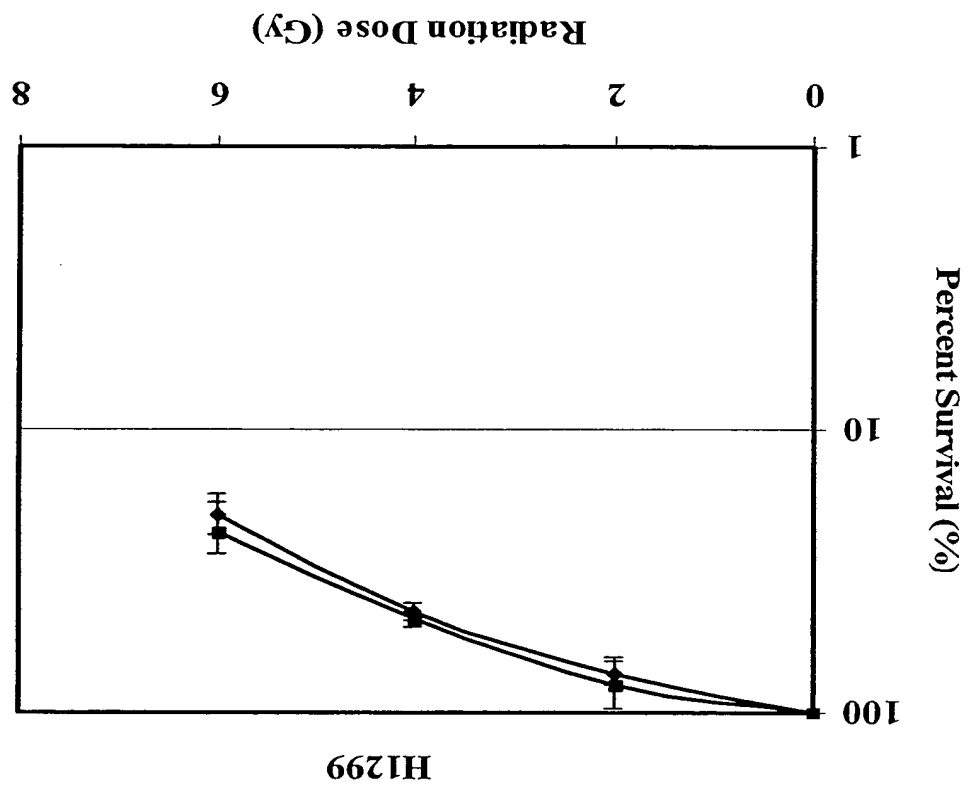
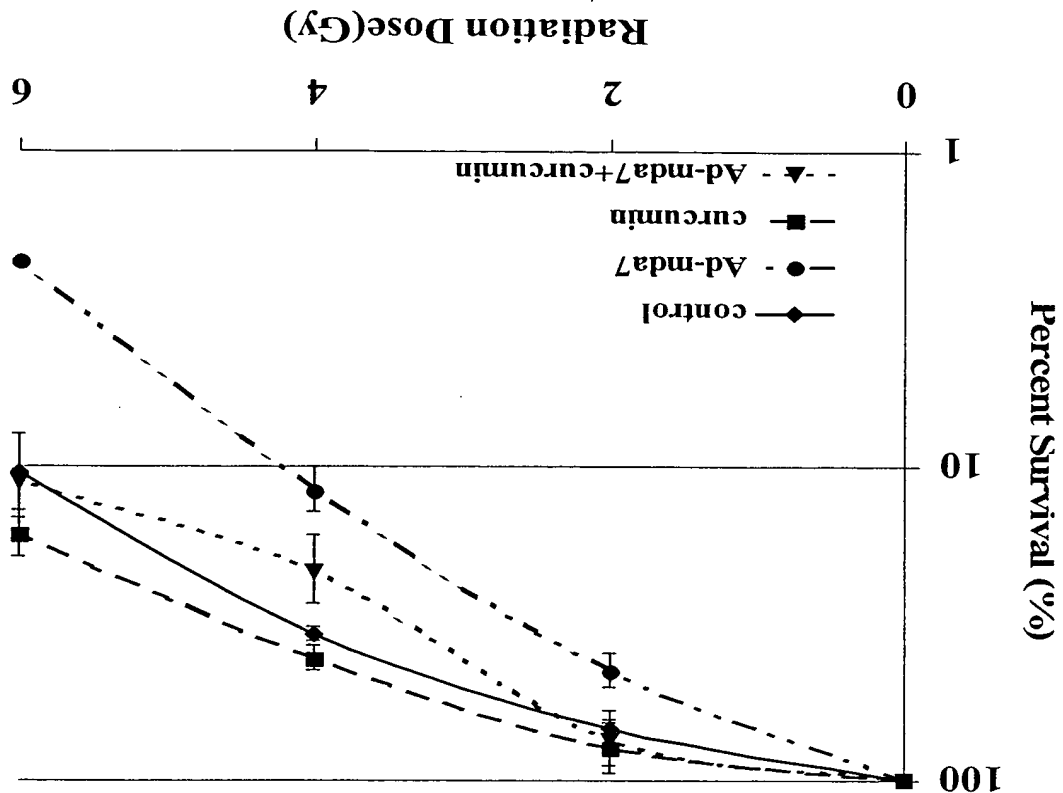
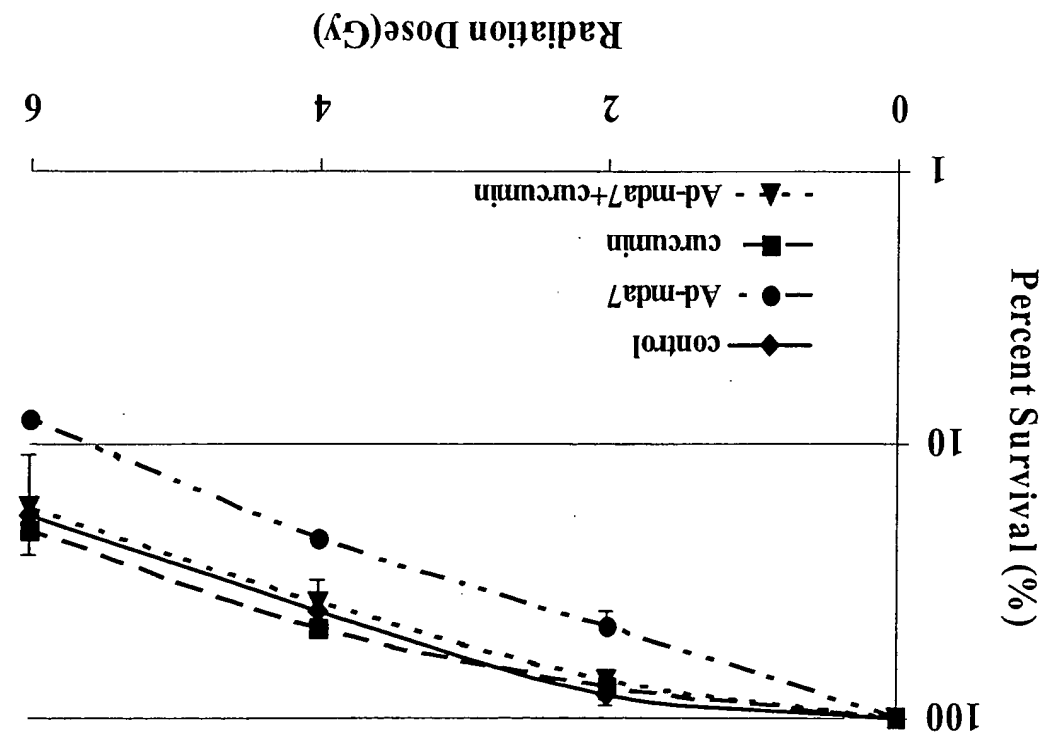


FIG. 23



A549



H1299

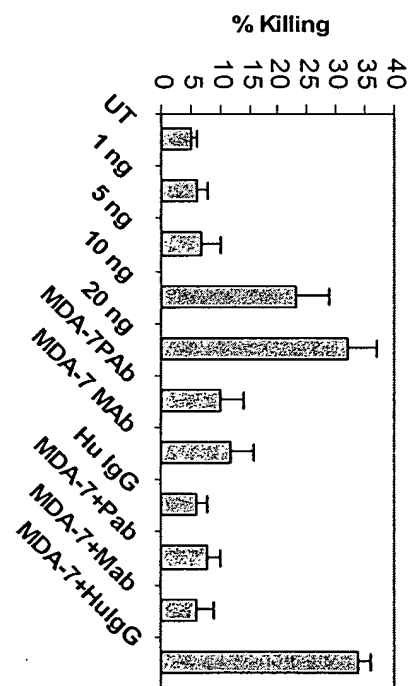


FIG. 24

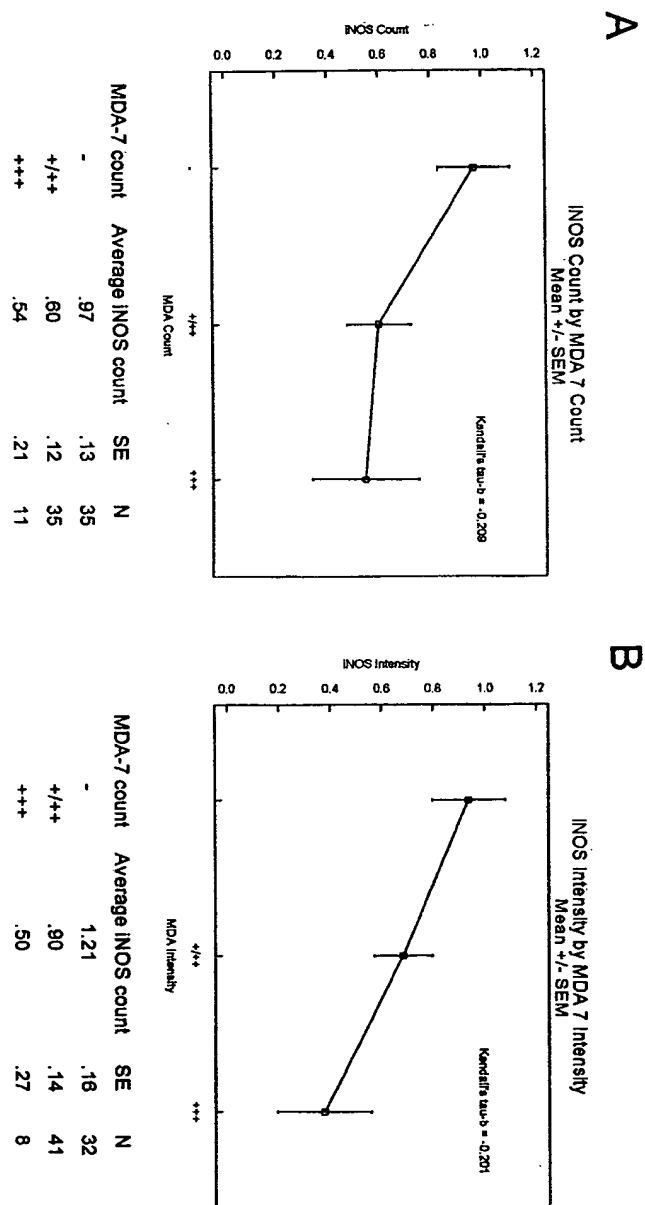


FIG. 25

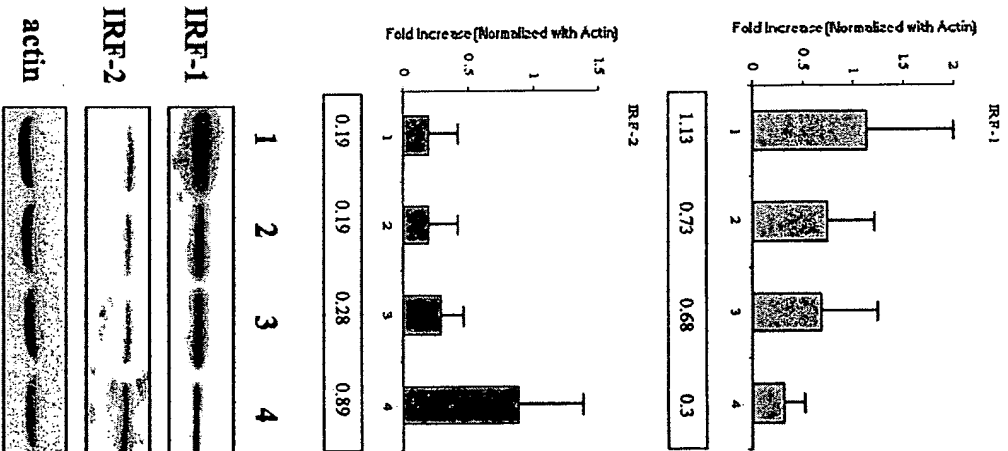


FIG. 26

FIG. 27

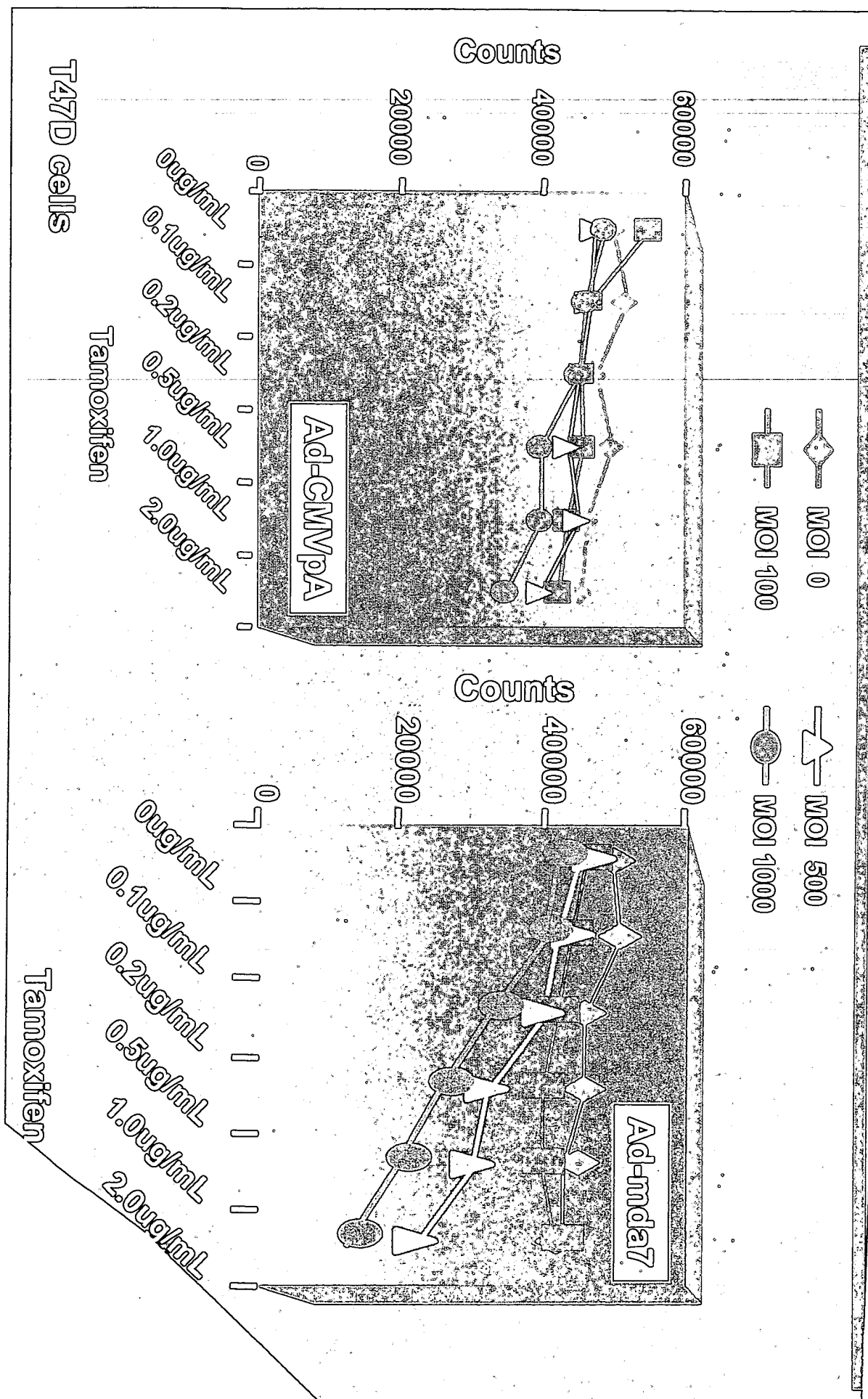


FIG. 28

	<u>IL-6</u>	<u>IFN-γ</u>	<u>IL-10</u>	<u>GM-CSF</u>	<u>s.Fas</u>	<u>IL-1β</u>	<u>TNF-α</u>	<u>pSTAT3</u>
Ad-	++	++	decrease	+/-	++	-	-	++
mda7								
MDA-7	+	+++	decrease	n.d.	n.d.	n.d.	n.d.	++

+ -> +++: increased cytokine secretion compared to Ad-luc control.

- : no change; n.d.: not done.

Cytokine levels were evaluated using ELISA from cultured cell supernatants taken 24-72 hr post treatment.
pSTAT3 results were analyzed 4hr after addition of MDA-7 protein and 24 hr after Ad-mda7 treatment using IHC.

Effect of Ad-mda7 on A549 Lung Metastasis

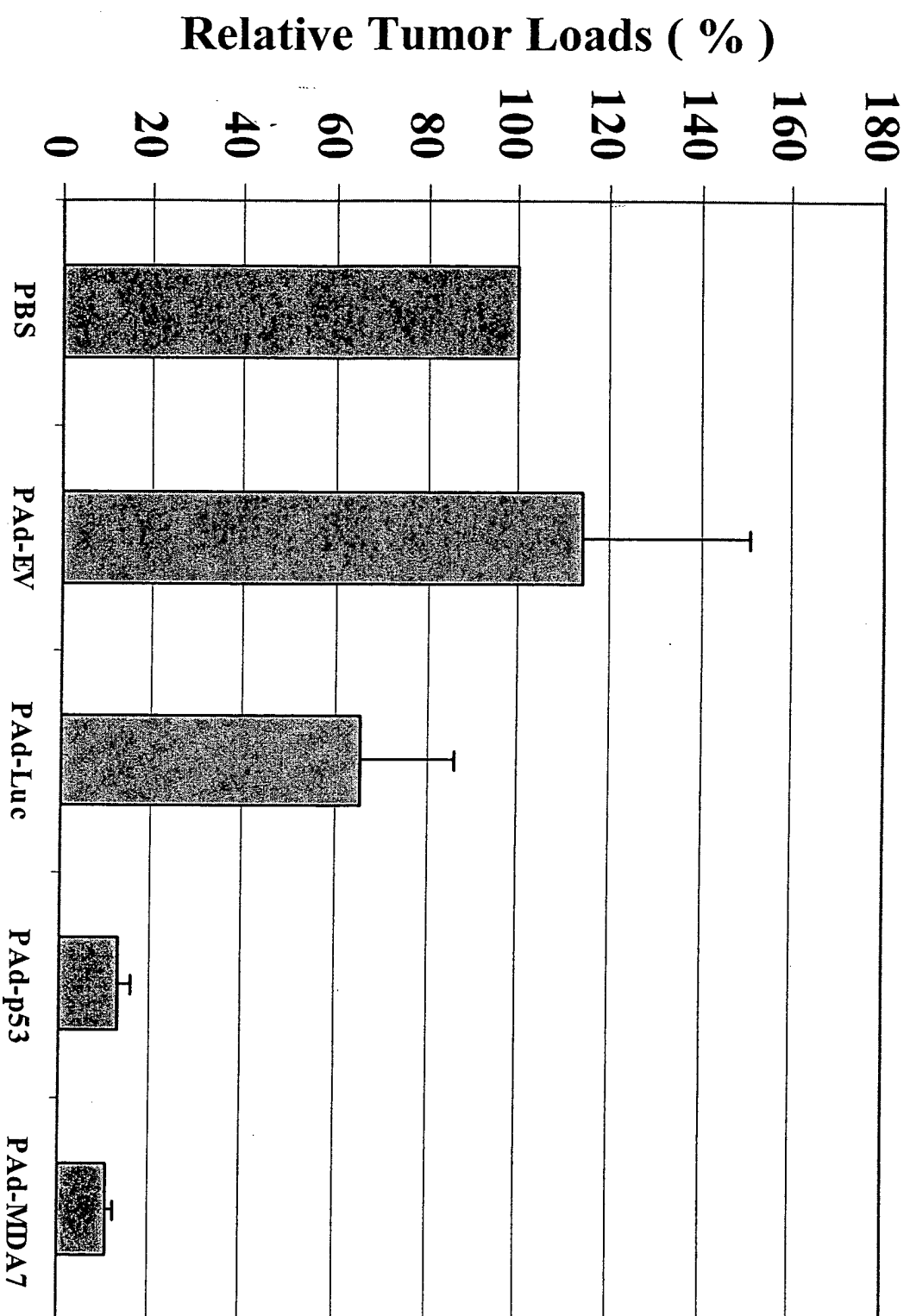


FIG. 29

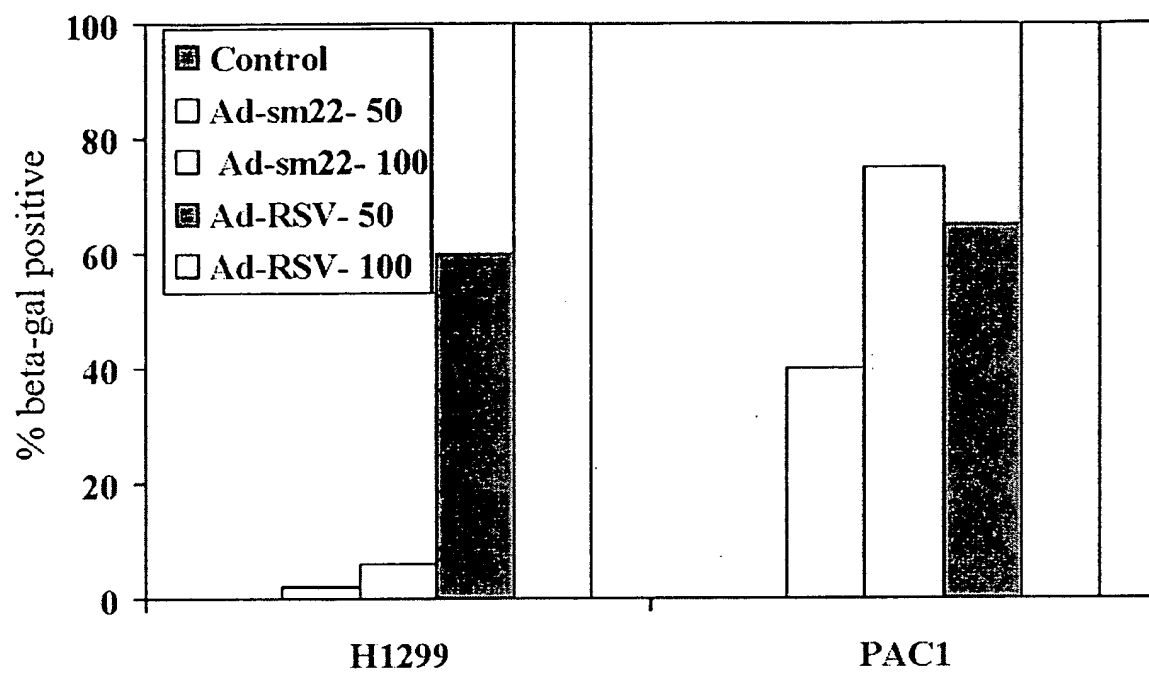


FIG. 30

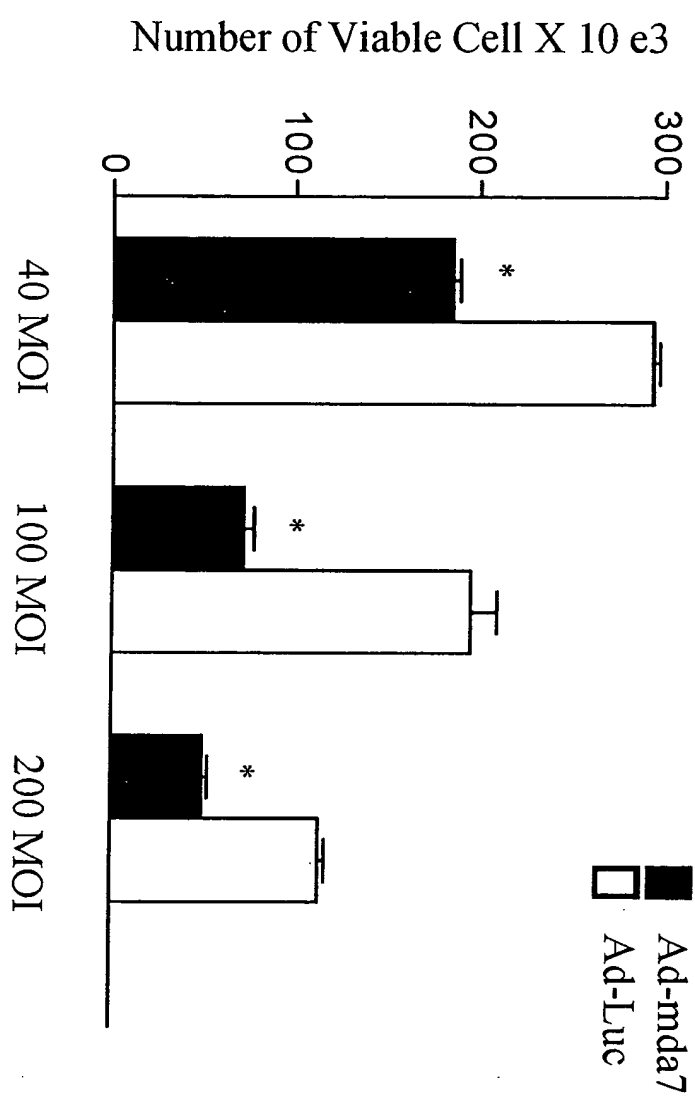


FIG. 31

A

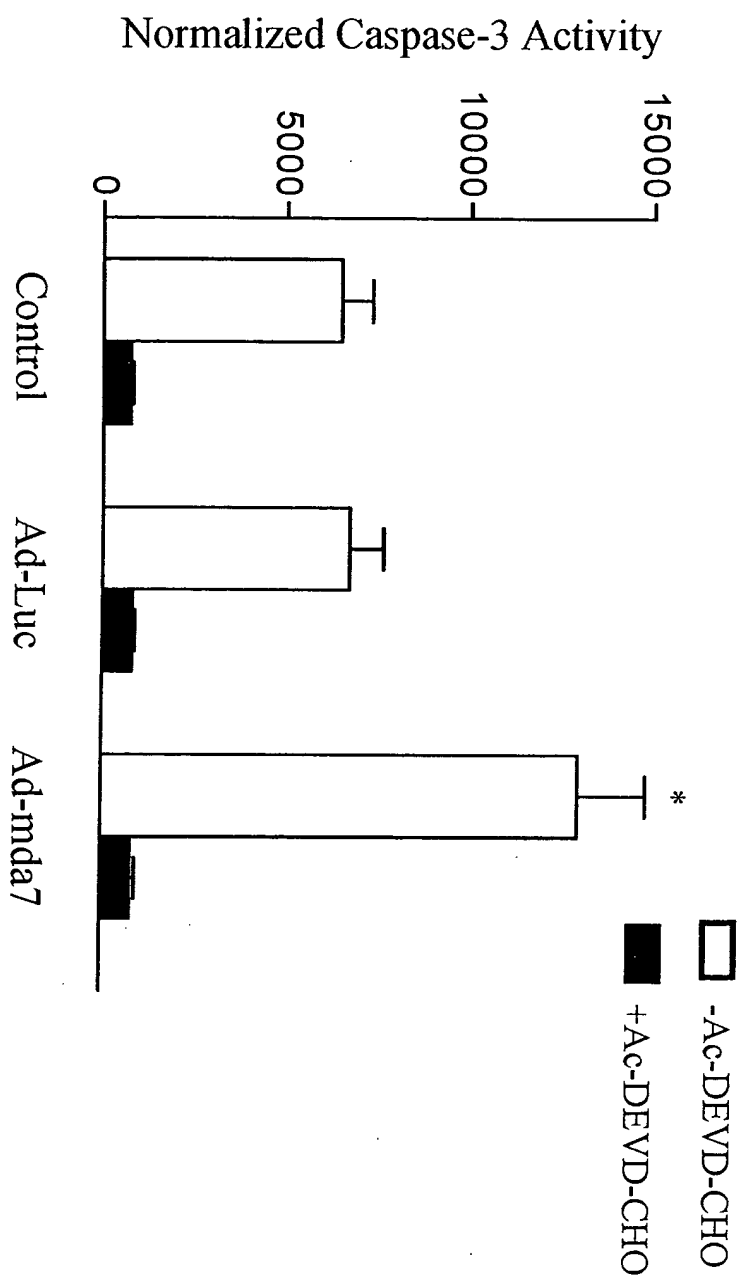


FIG. 32A

B

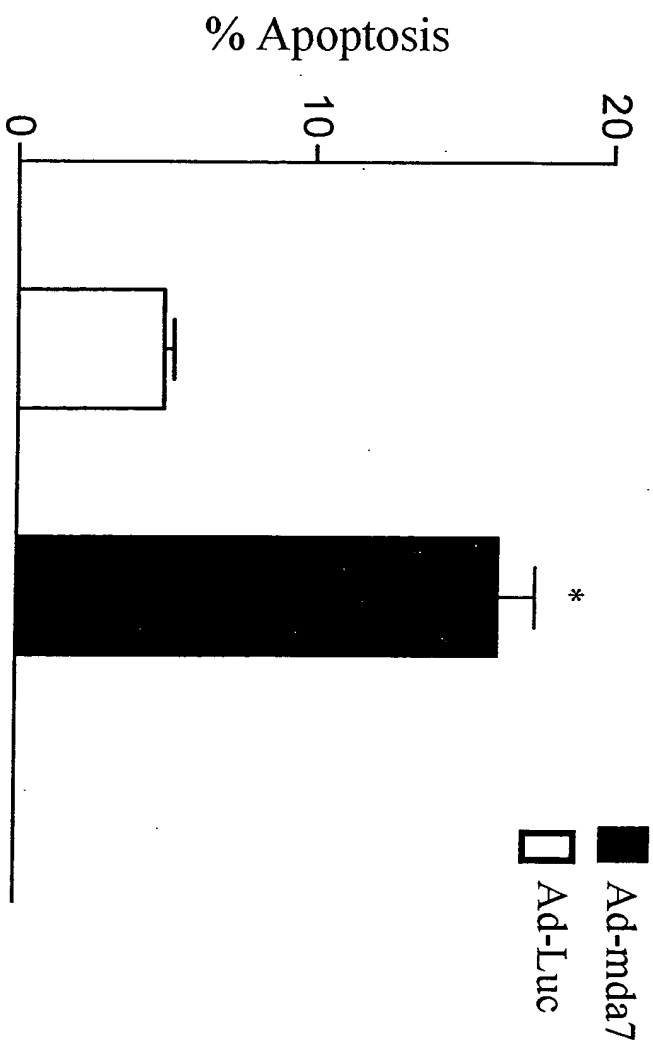


FIG. 32B

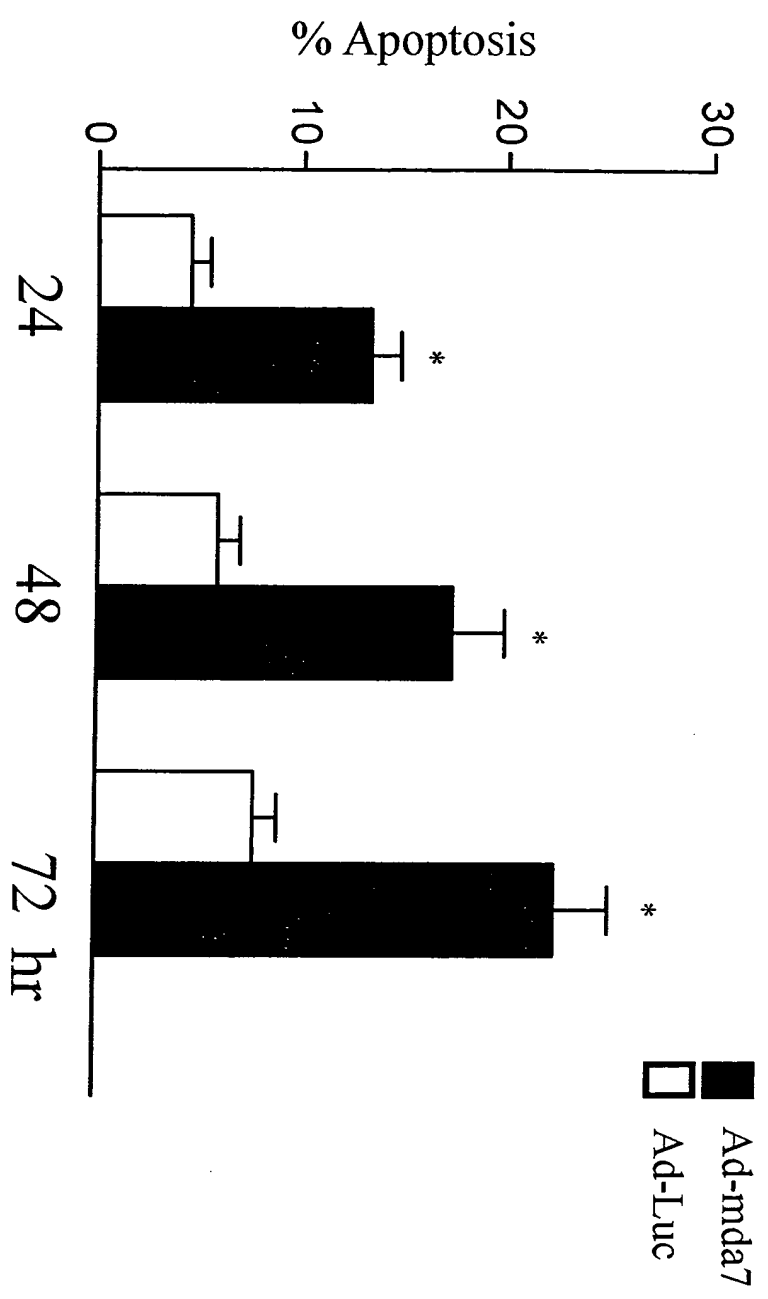


FIG. 32C

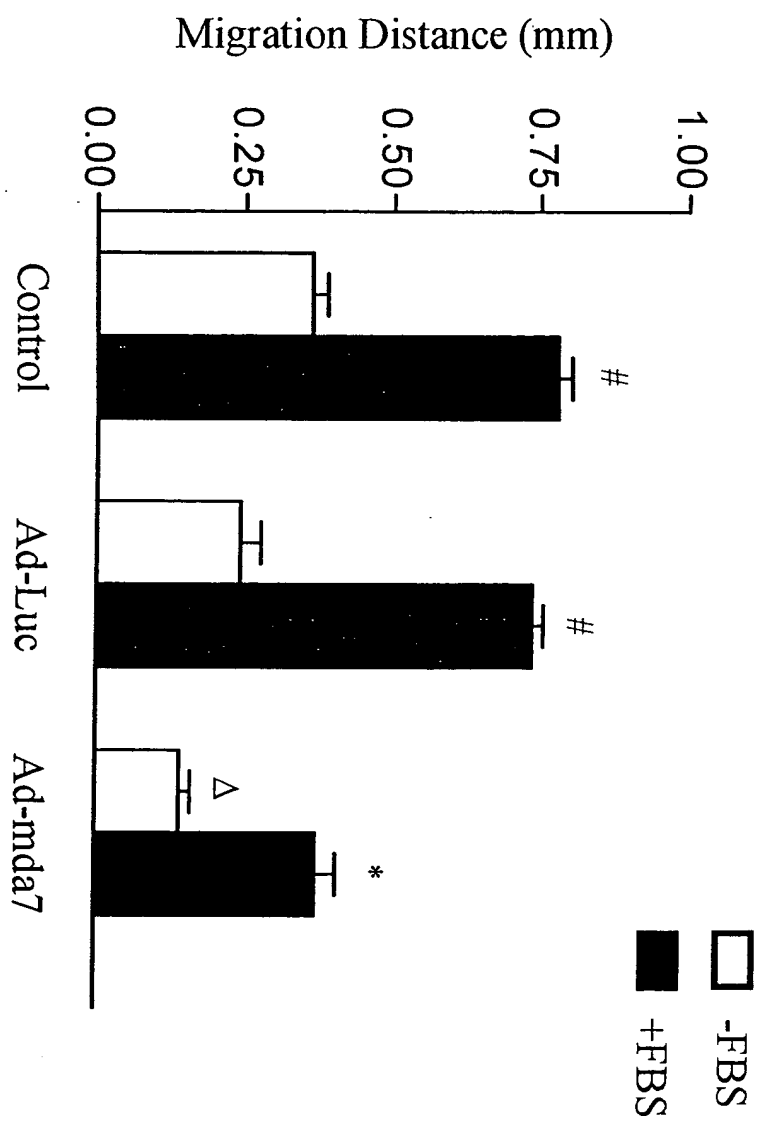


FIG. 33

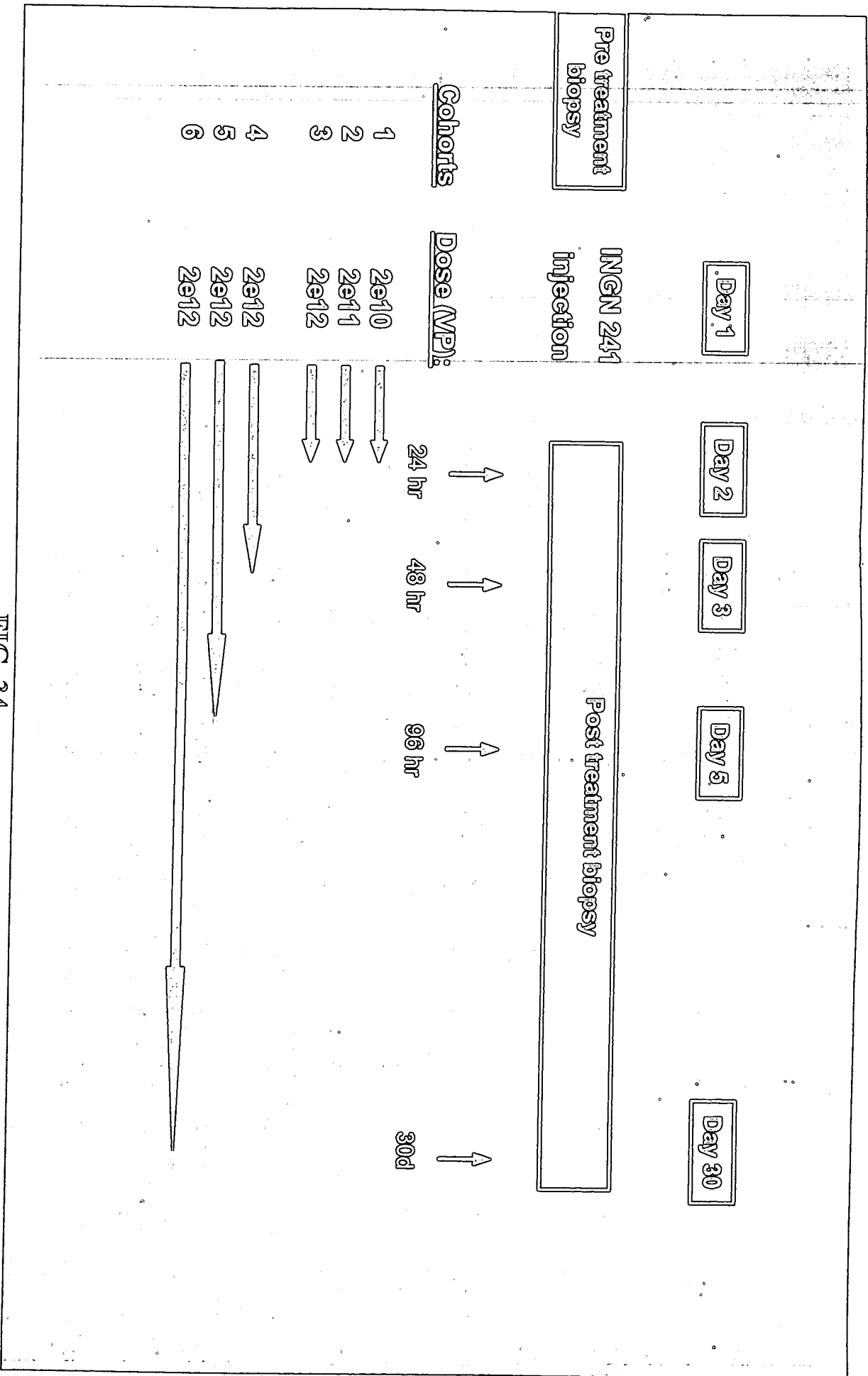


FIG. 34

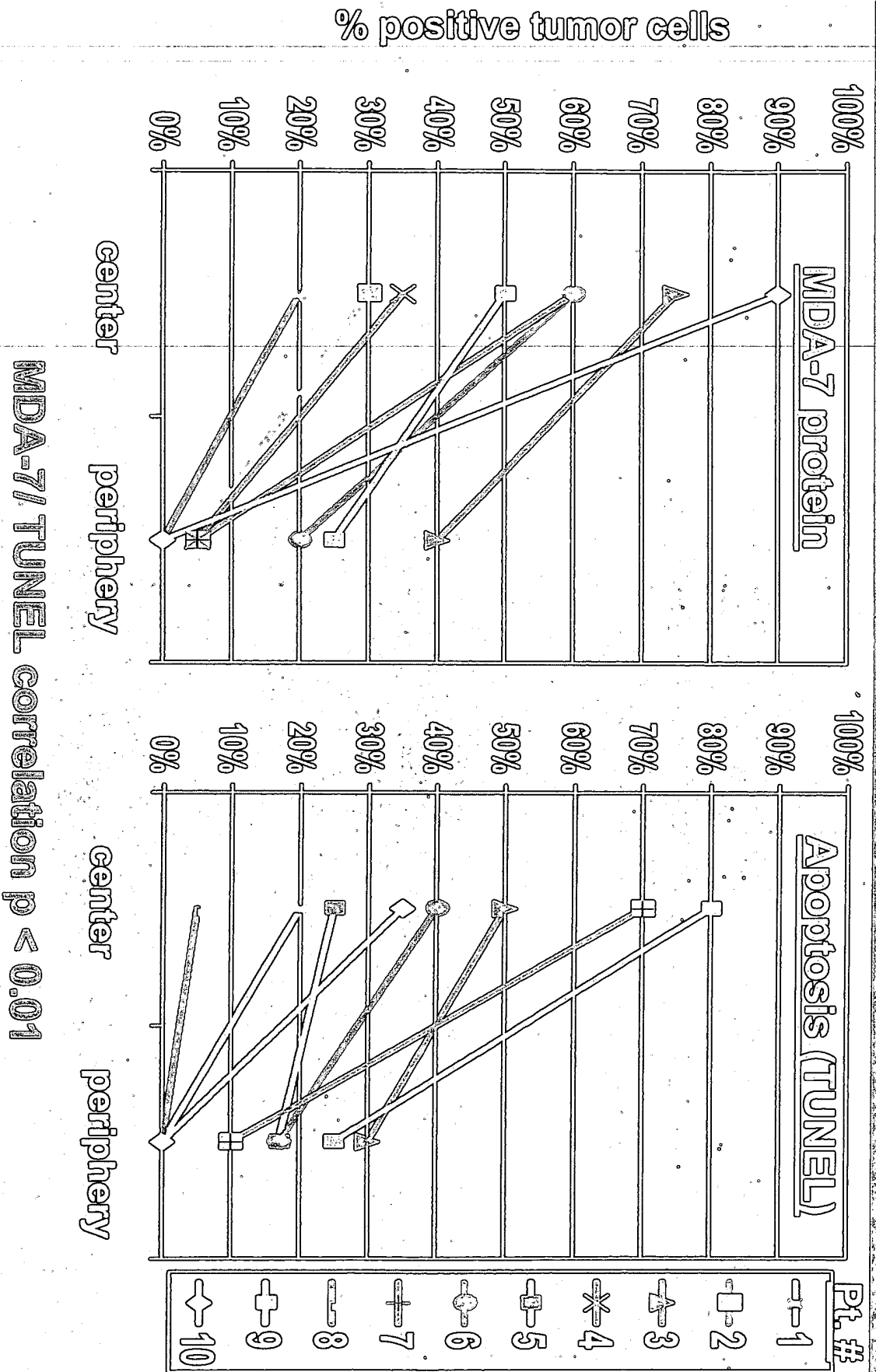
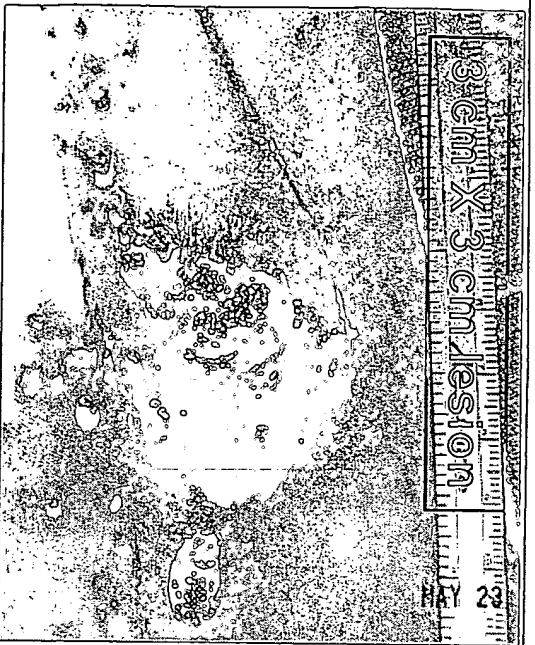


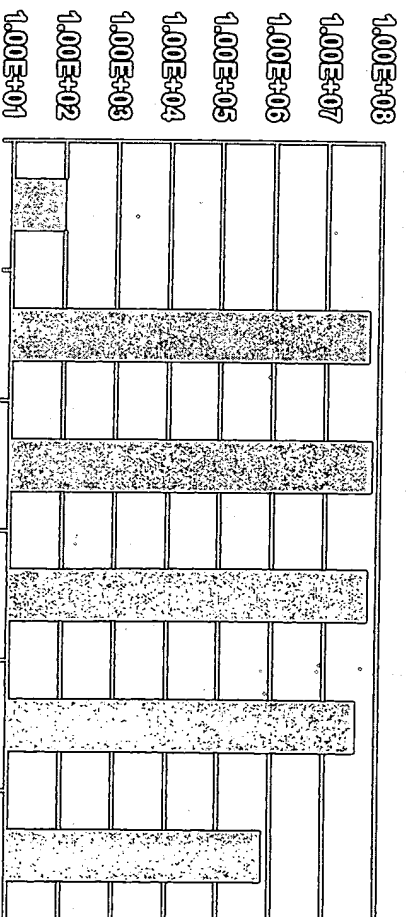
FIG. 35



Distance from center of lesion:

0 mm 3 6 9 12mm

INGN 241
DNA
Expression
#copies/ug



MDA-7 protein expression

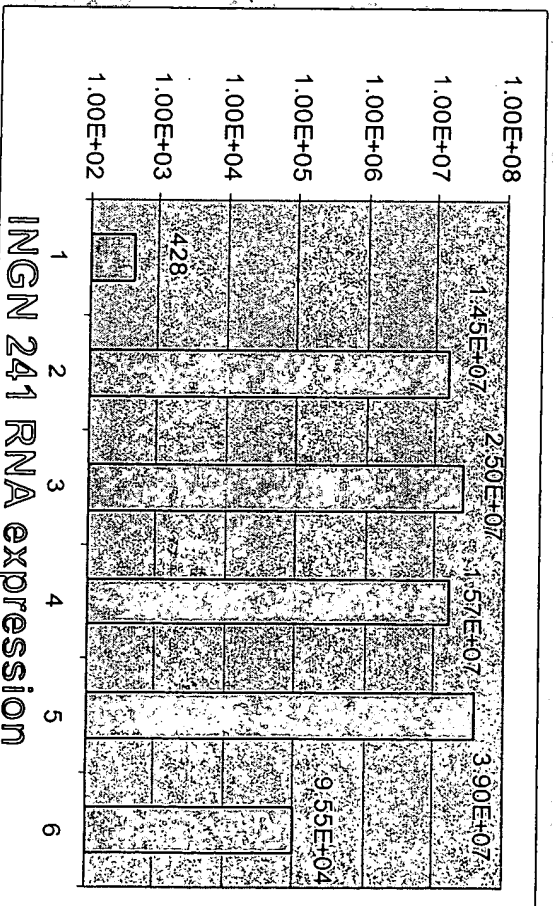
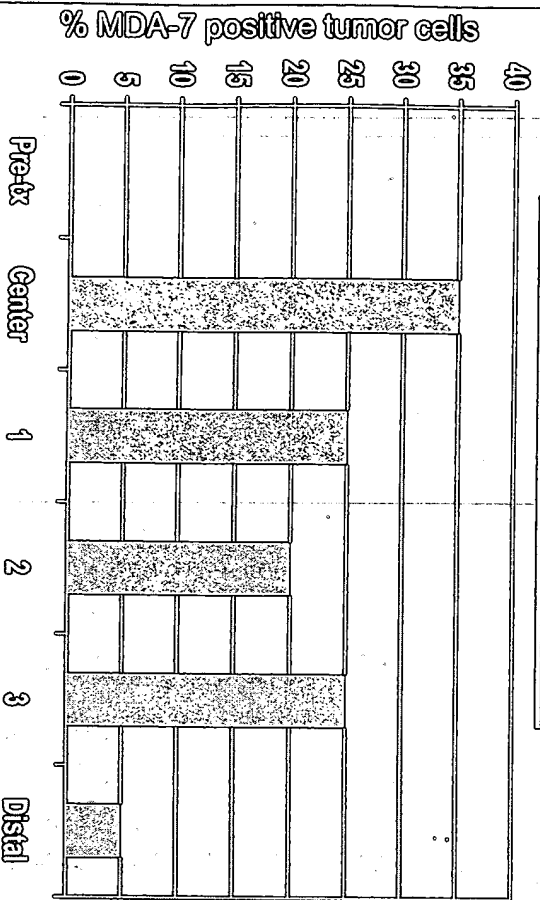


FIG. 36

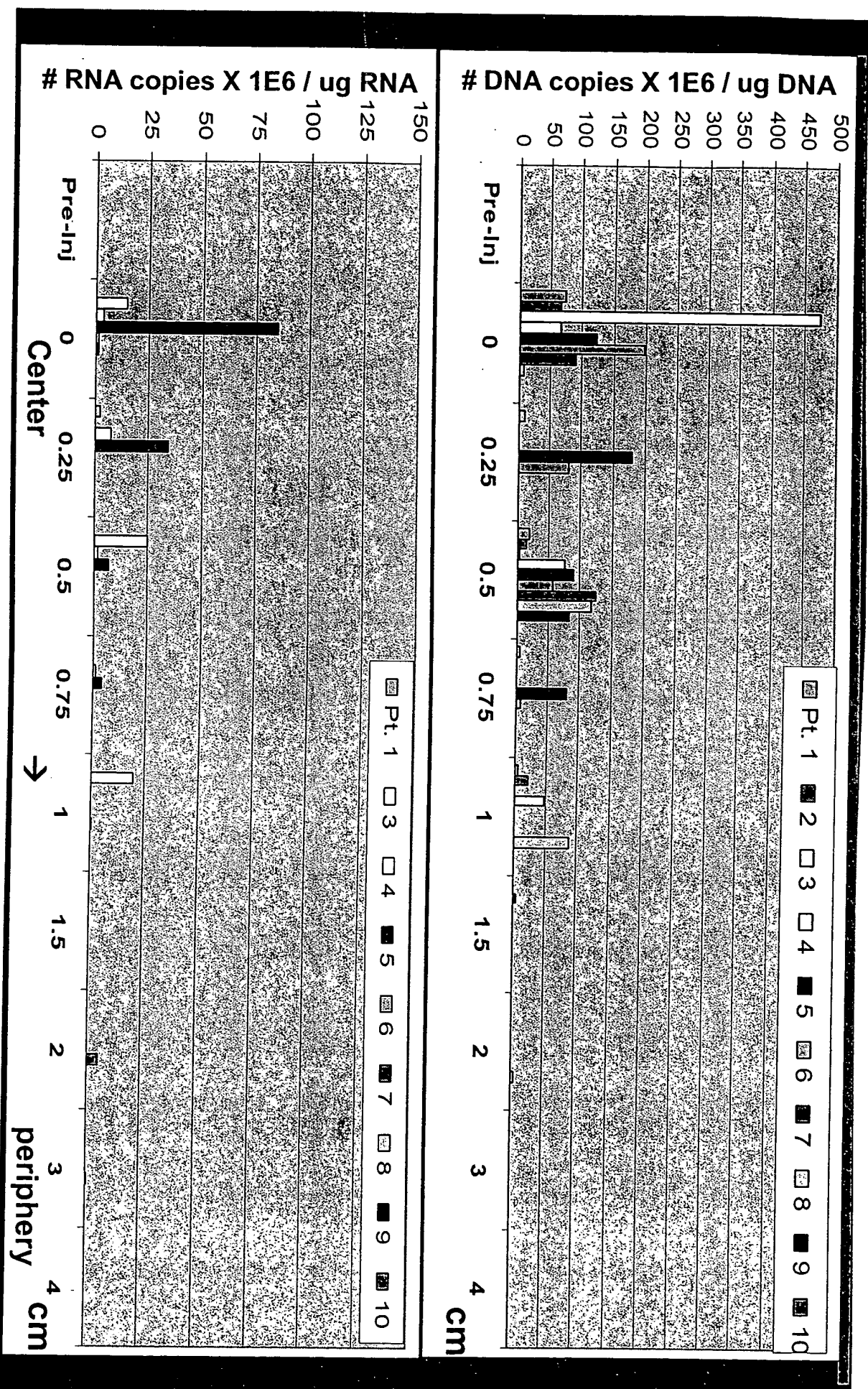


FIG. 37

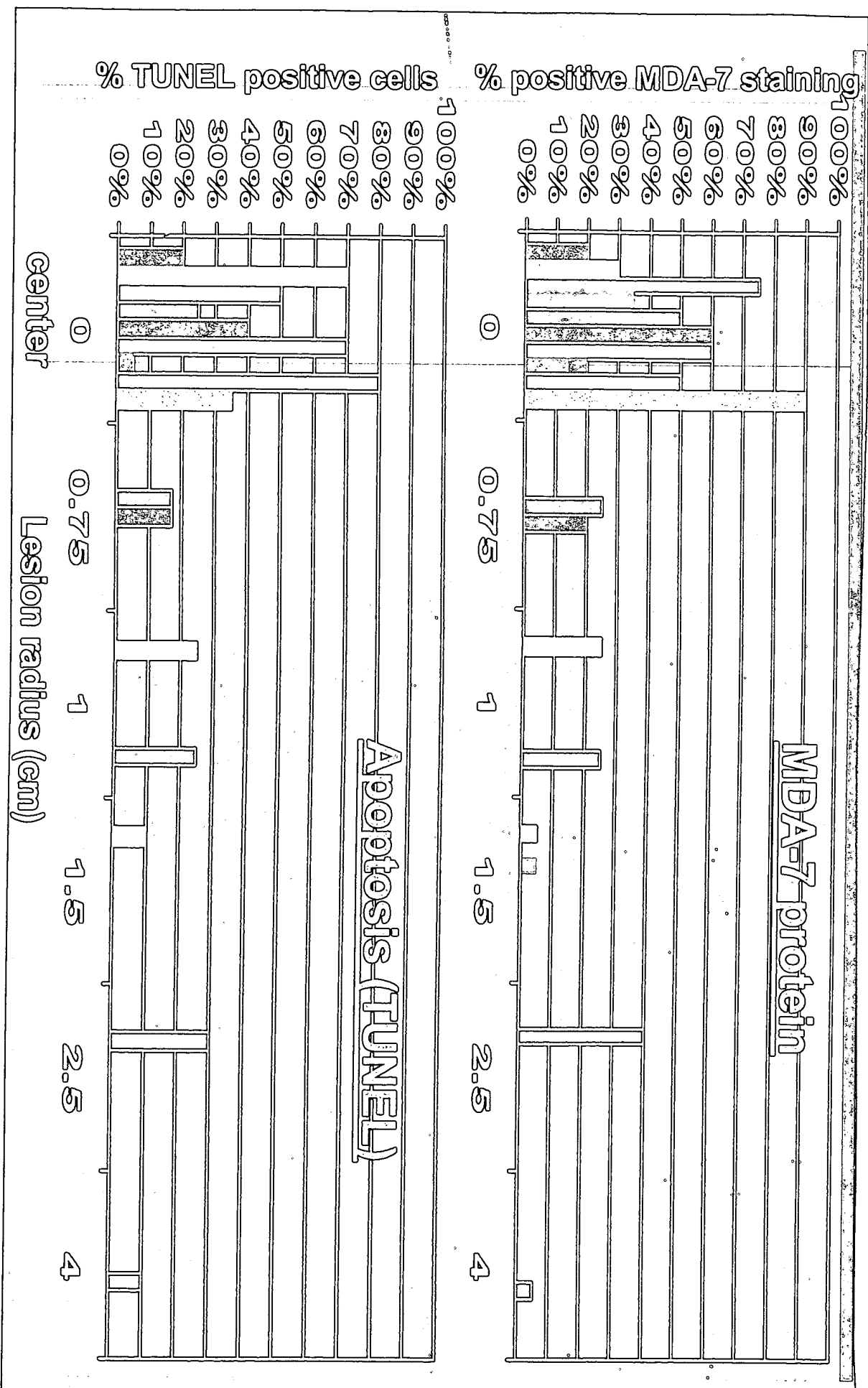


FIG. 38

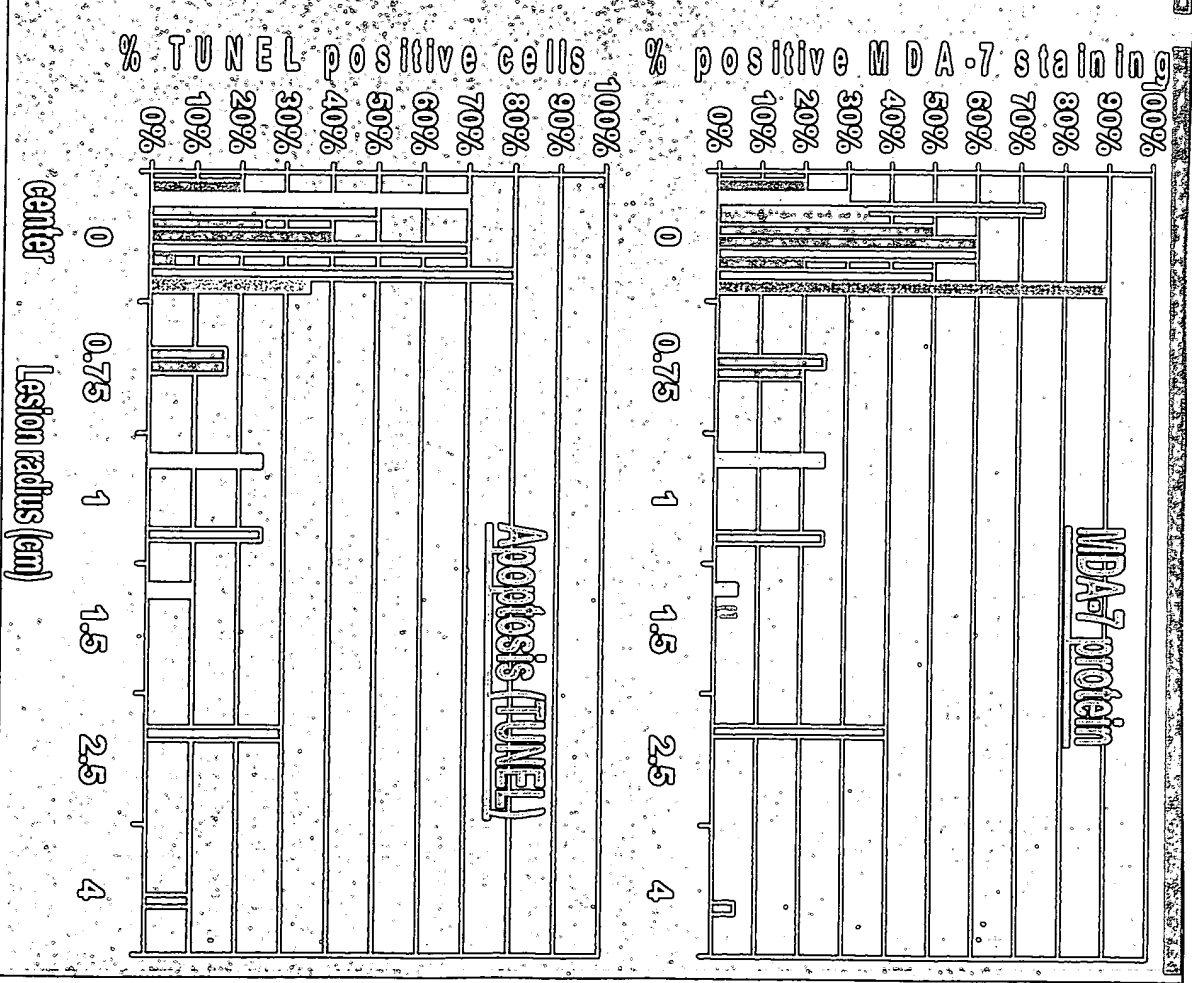
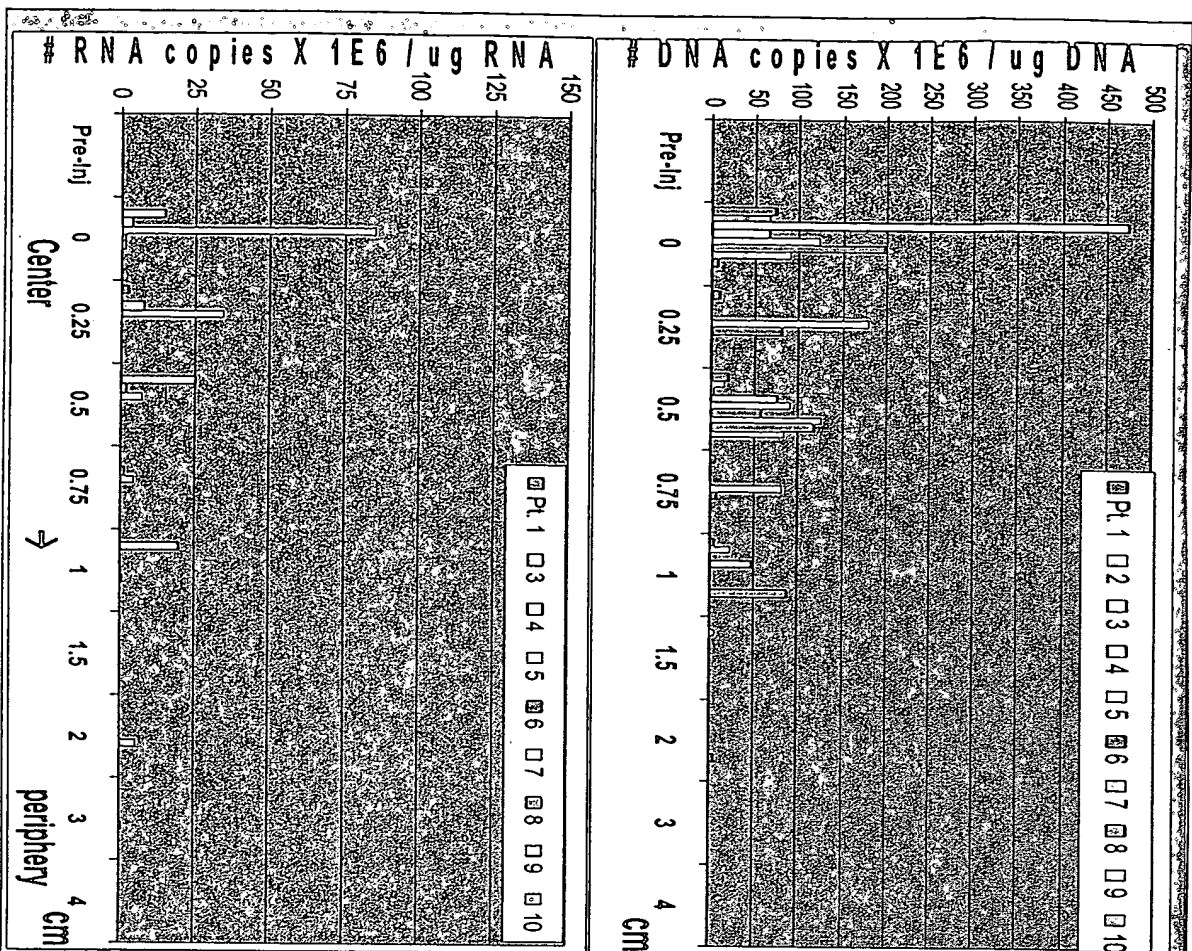


FIG. 39

Av. copies/cell: 0.001

740

900

1

0.04

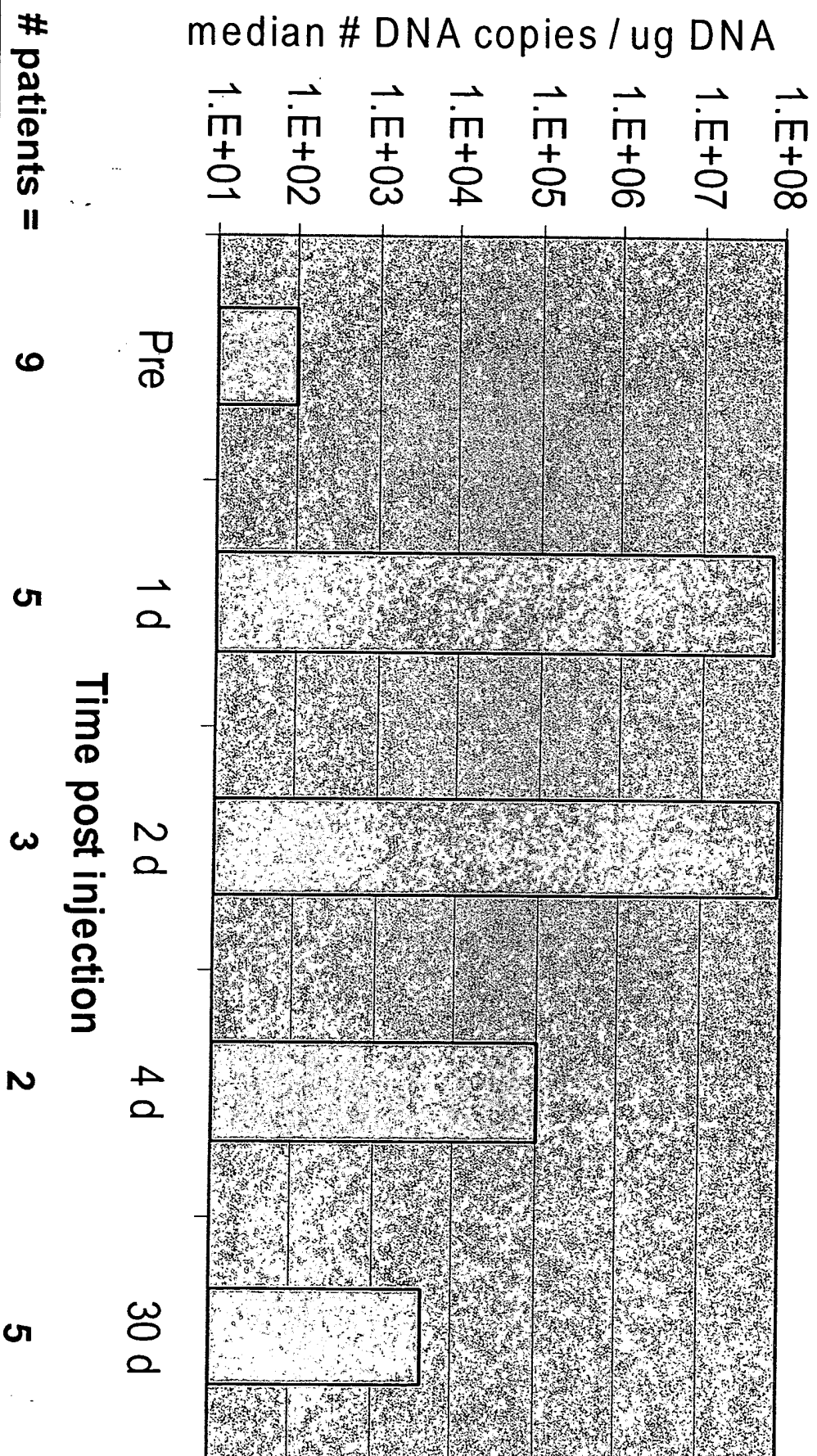


FIG. 40

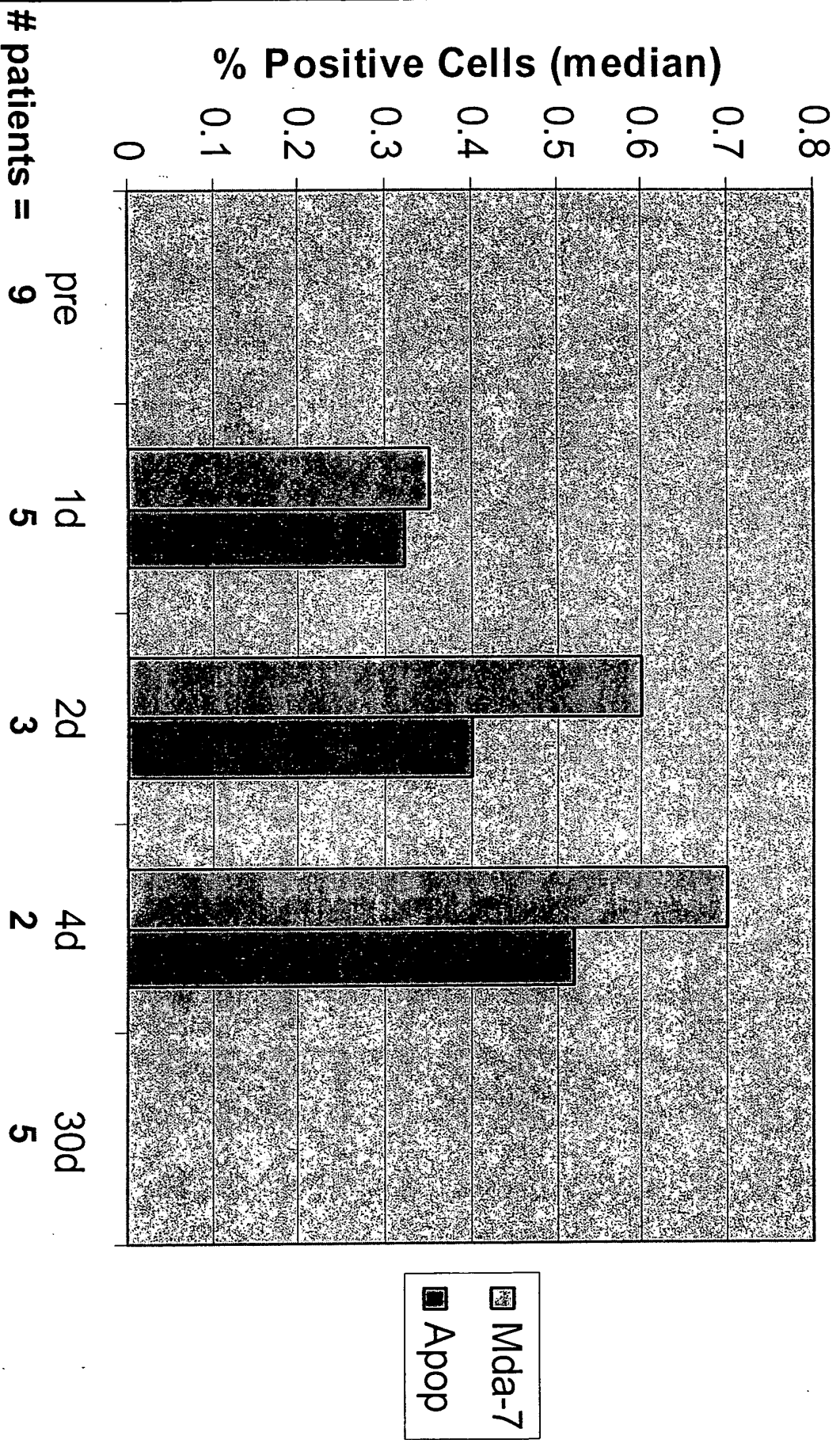


FIG. 41

Single Dose (2E12 vp)		Clinical Activity (Y/N)			Comment
Patient	Primary Histology	# injections	Local	Remote	
71	Renal Cell Ca	1	N	N	Withdraw prior to day 30
72	TCC Bladder	1	N	N	
73	Melanoma	1	N	N	
74	Colo-Rectal	1	N	N	
75	SCCHN	1	N	N	
76	SCCHN	1	N	N	Withdraw prior to day 30
77	SCCHN	1	N	N	
Repeat Dose (2E12 vp biweekly x3)					
81	AdenoCa	3	-	-	Withdraw
83	Melanoma	12	Y*	Y**	CR
84	Melanoma	12	N	N	Stable Disease
85	SCCHN	6	Y	N	Central necrosis
86	NSCLC	3	-	-	Not eval
87	SCCHN	6	Y	pending	On study
88	Melanoma	6	Y	pending	On study

* Three lesions treated consecutively: pCR in 1st, cInCR in 2nd, regression in 3rd

** marked erythema around remote cutaneous lesion

*Three lesions treated consecutively: pCR in 1st, cInCR in 2nd, regression in 3rd
 **marked erythema around remote cutaneous lesion

FIG. 42

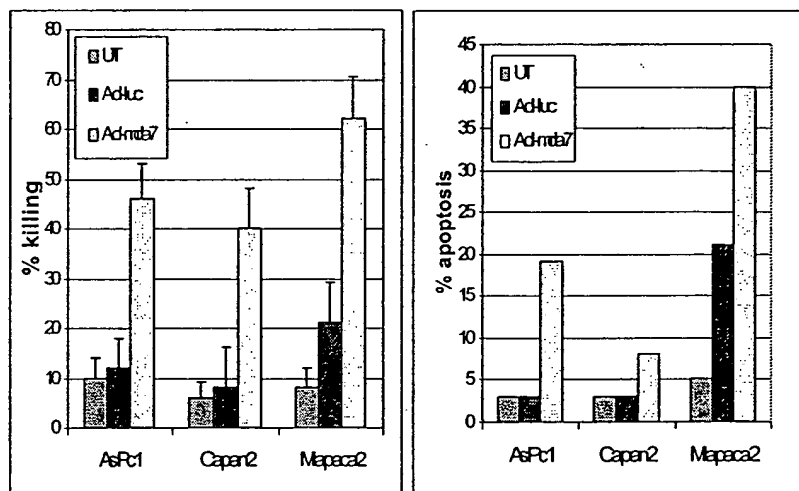


FIG. 43

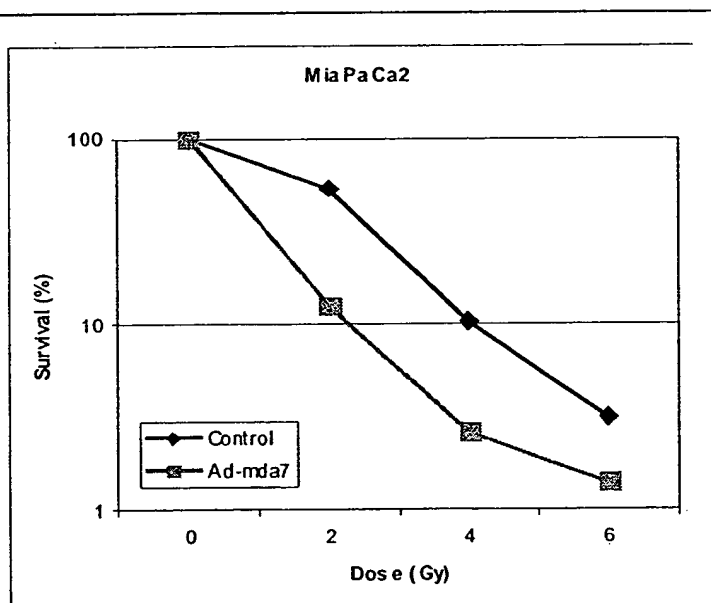


FIG. 44

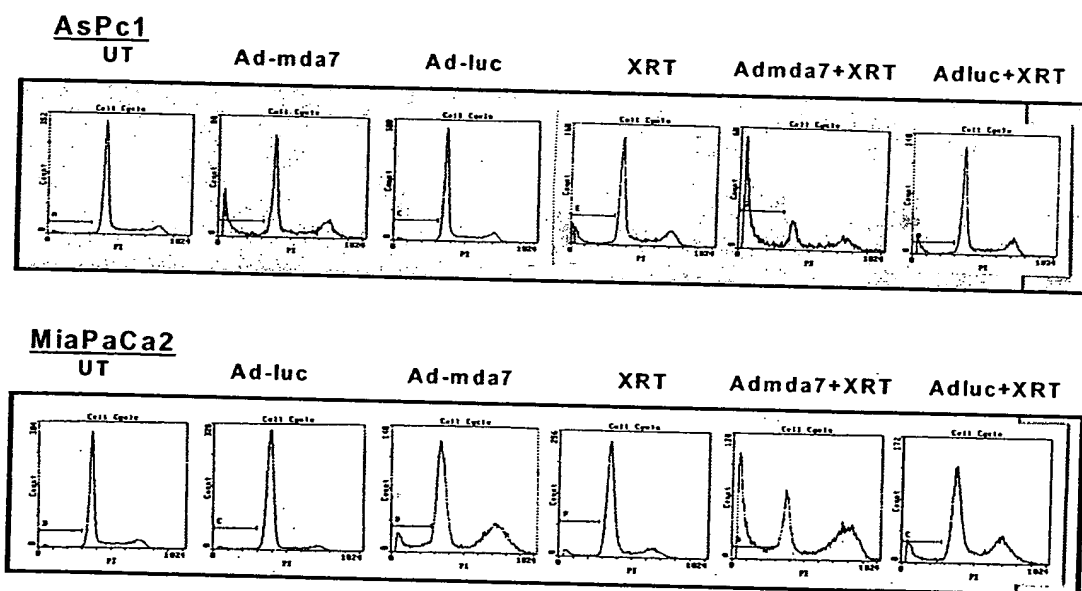


FIG. 45

48 hrs after infection

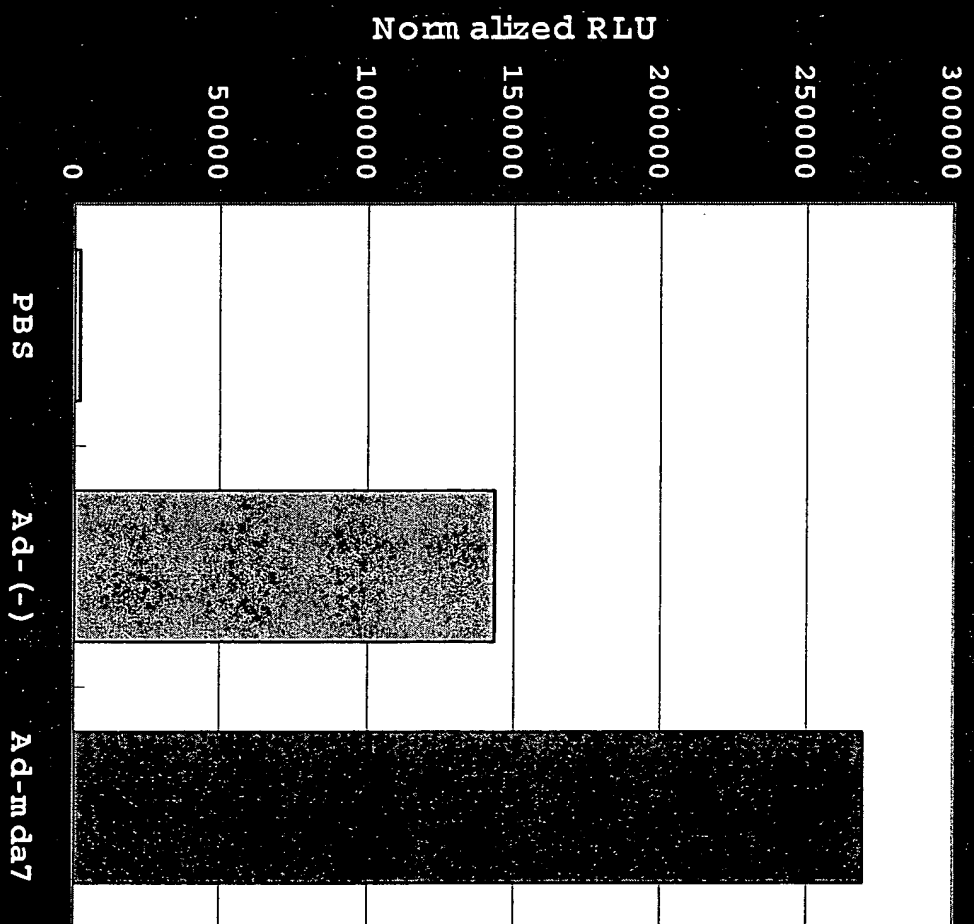


FIG. 46

H1299



Parental

neo

I-kB DN

clone 1

clone 2

clone 3

IC₅₀ value

Ad-mdm27

clone	(x10 ³ vp/cell)
neo	3.27 ± 1.1
clone1	2.58 ± 1.25
clone3	1.25 ± 0.3
clone3	3.98 ± 0.88

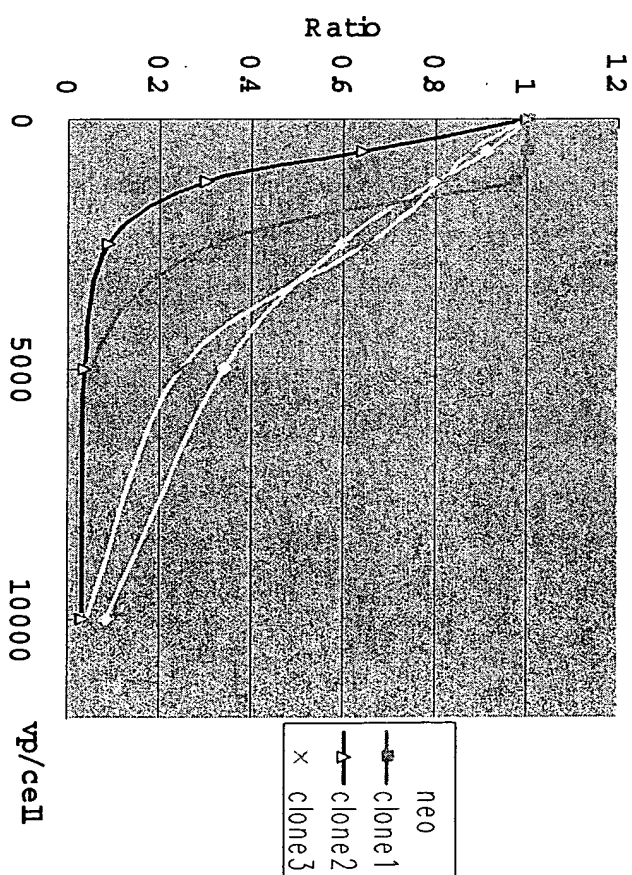


FIG. 47

H1299

72hrs after infection



neo mI-2Ba
PBS Ad-luc Ad-mda7 PBS Ad-luc Ad-mda7

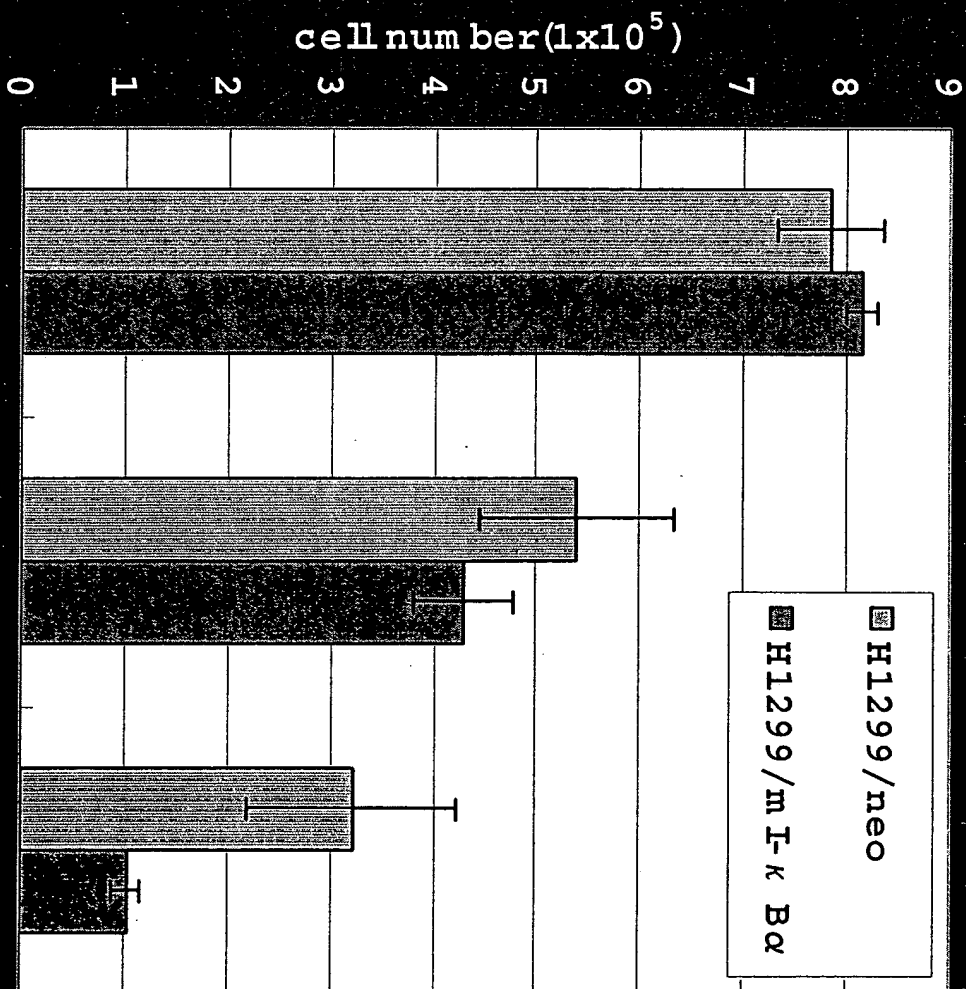


FIG. 48

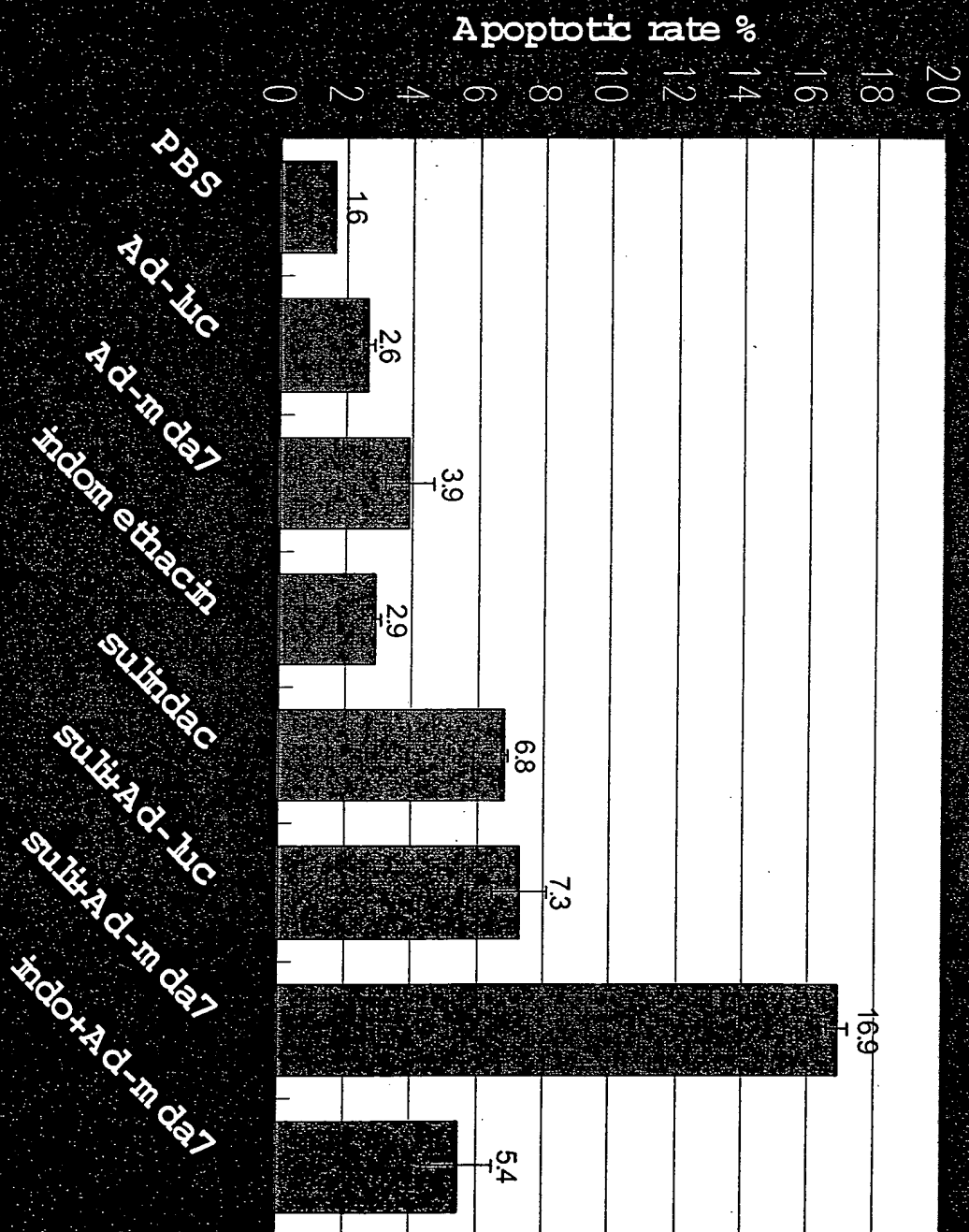


FIG. 49A

A

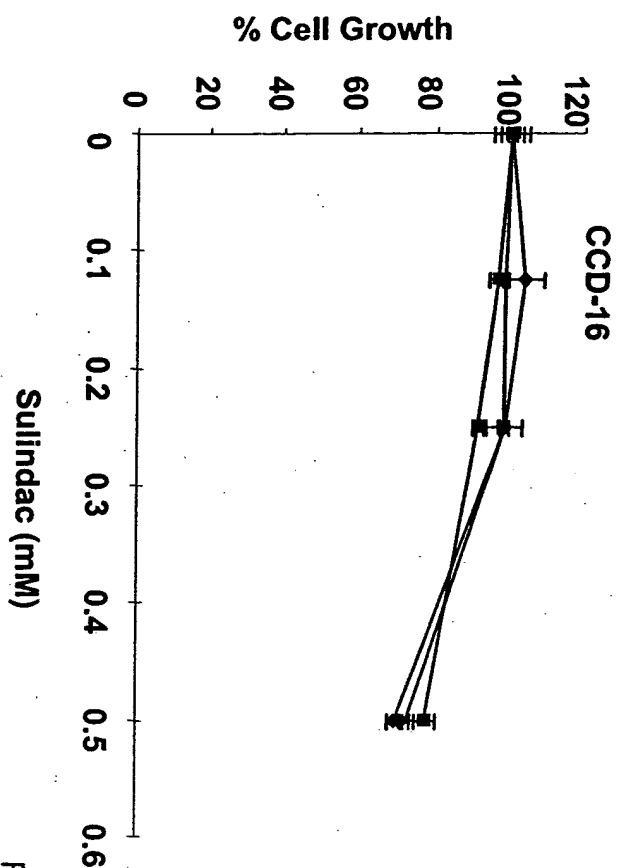
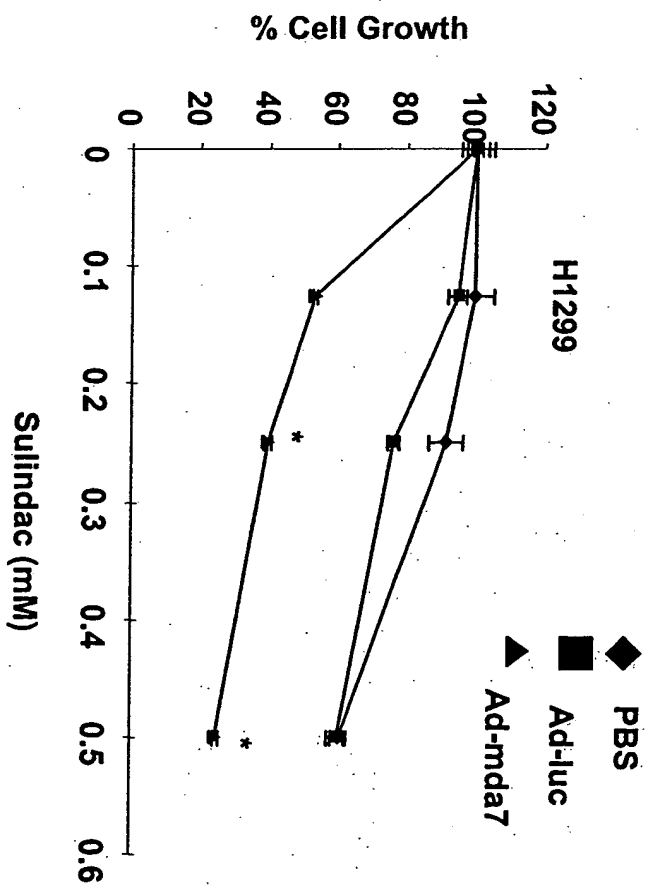
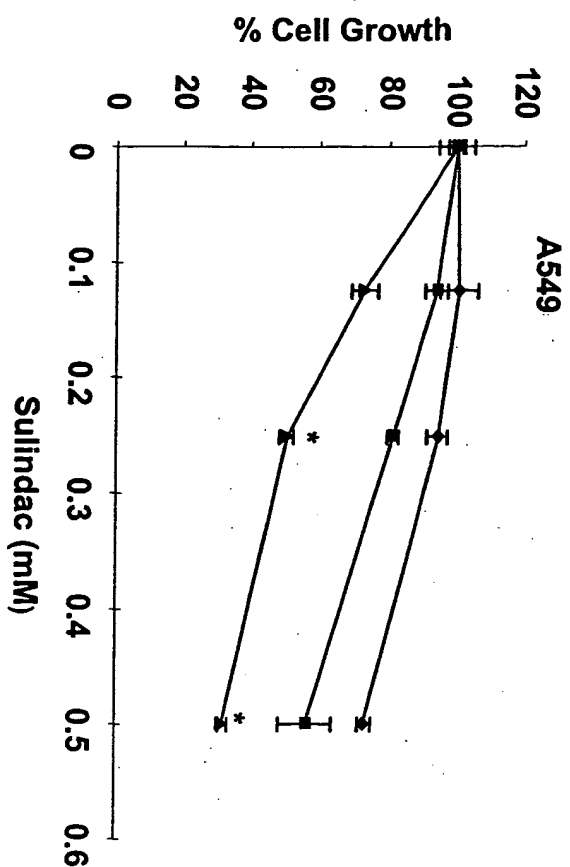


FIG. 49B

B

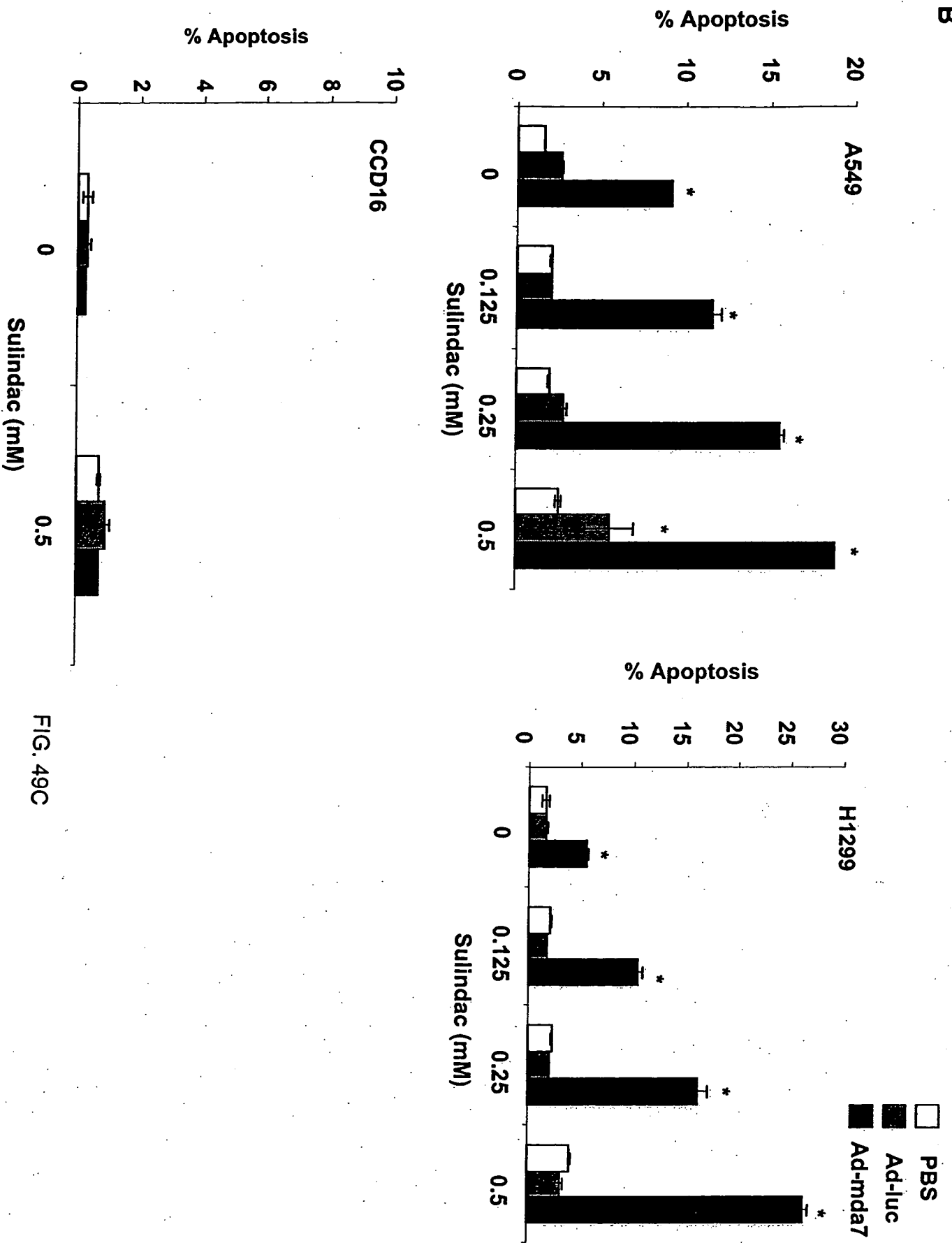


FIG. 49C

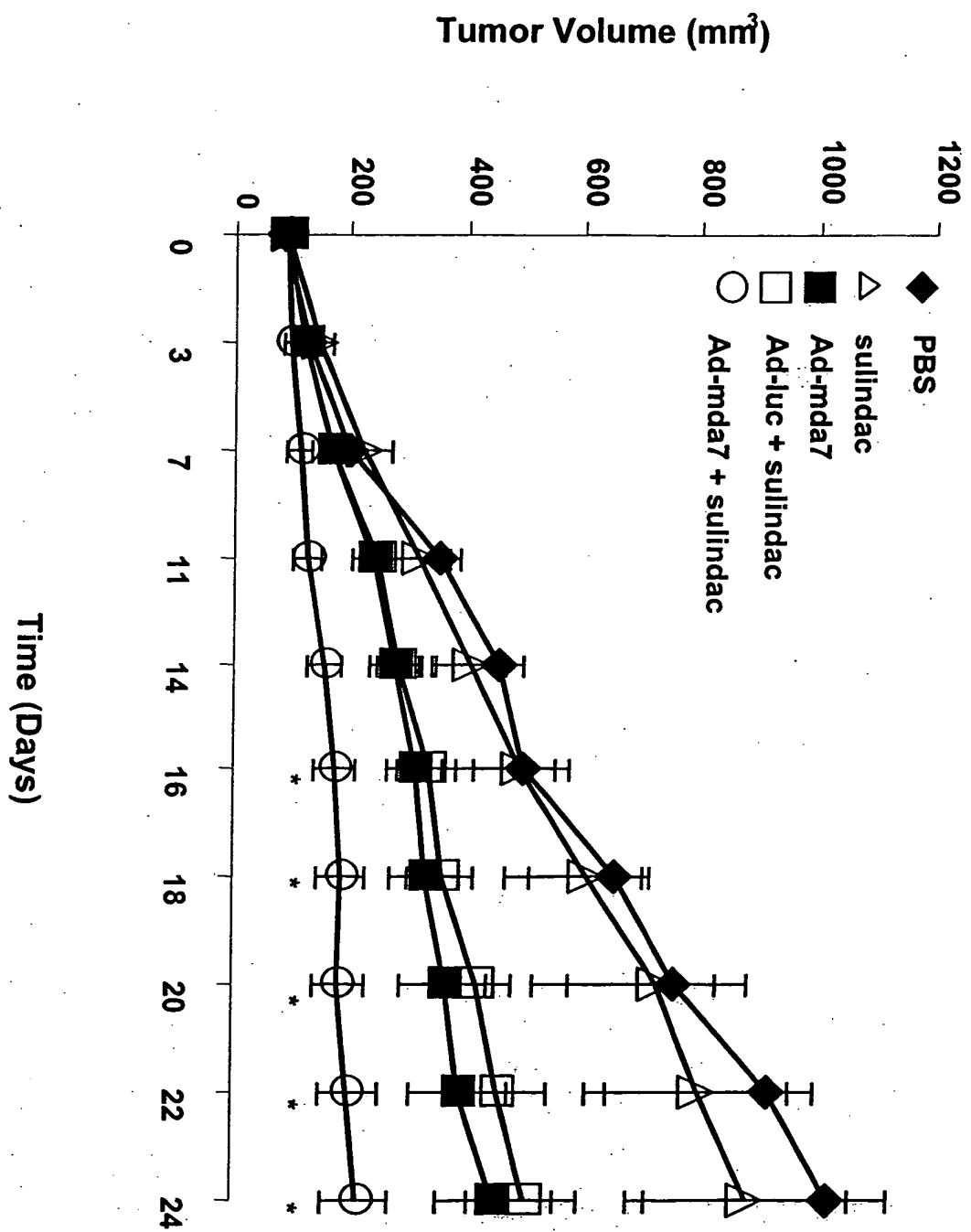


FIG. 49D

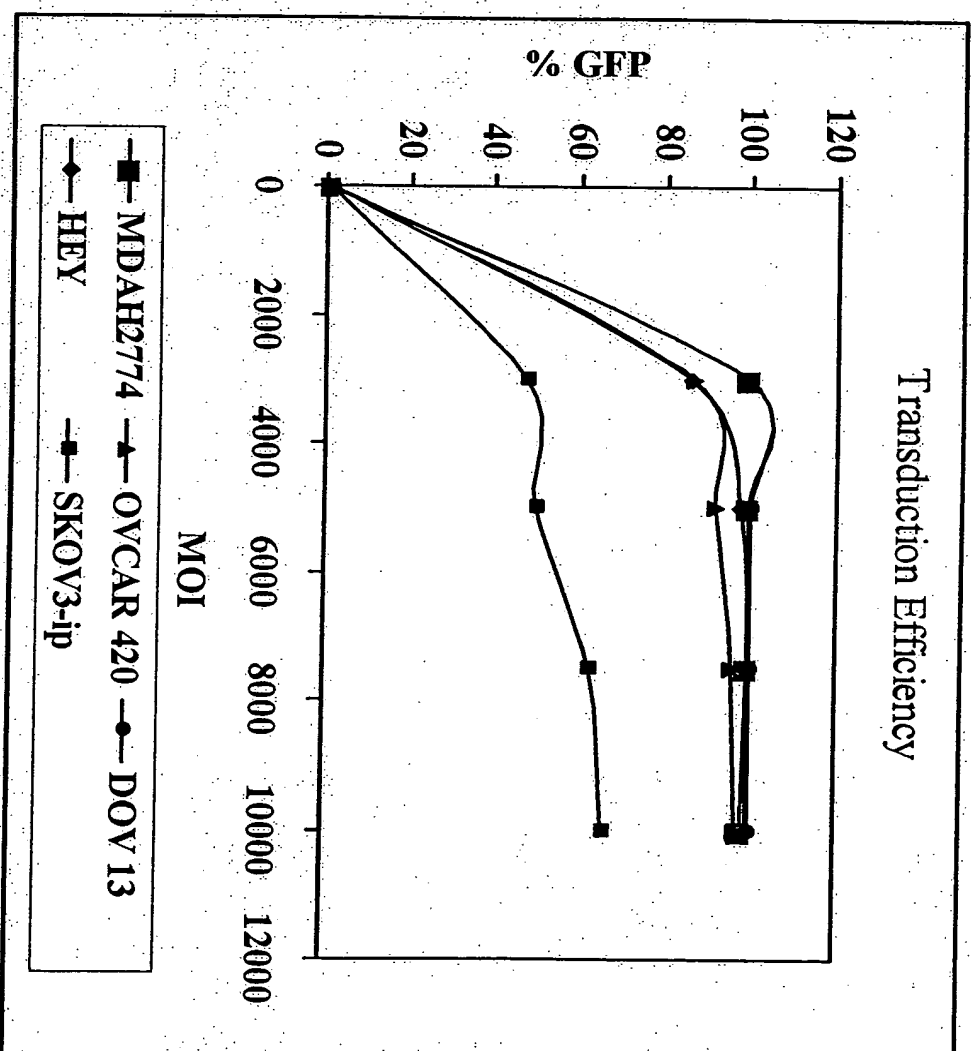


FIG. 50

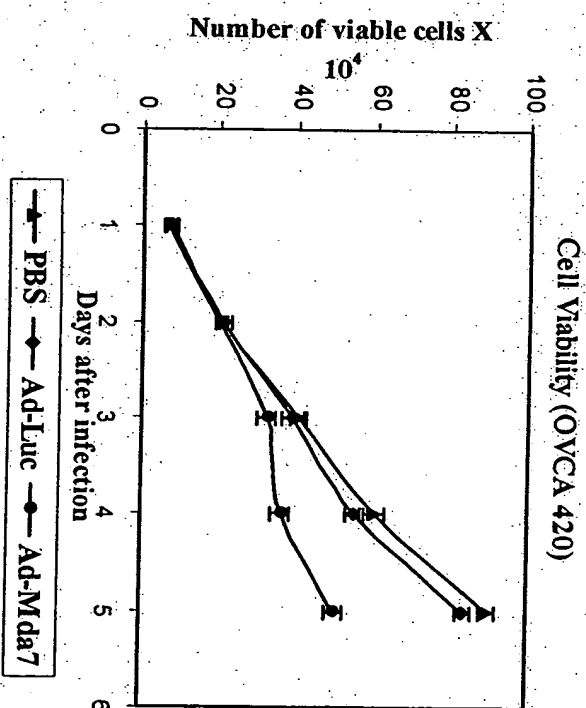
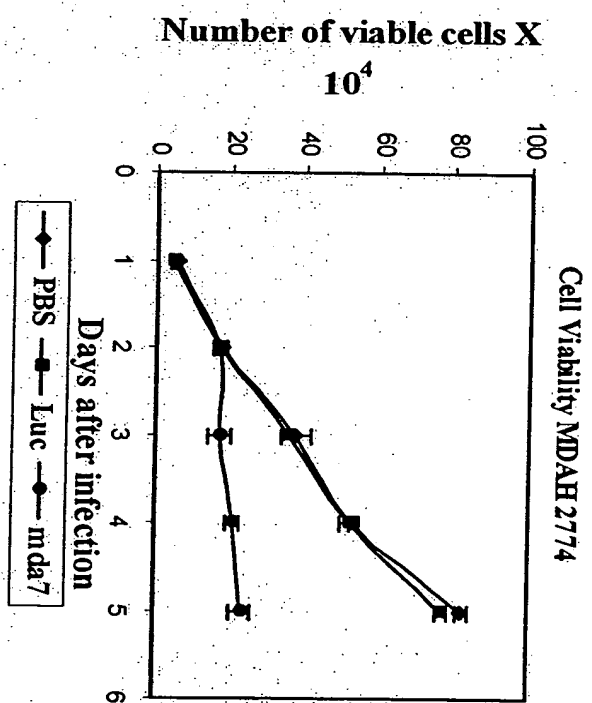
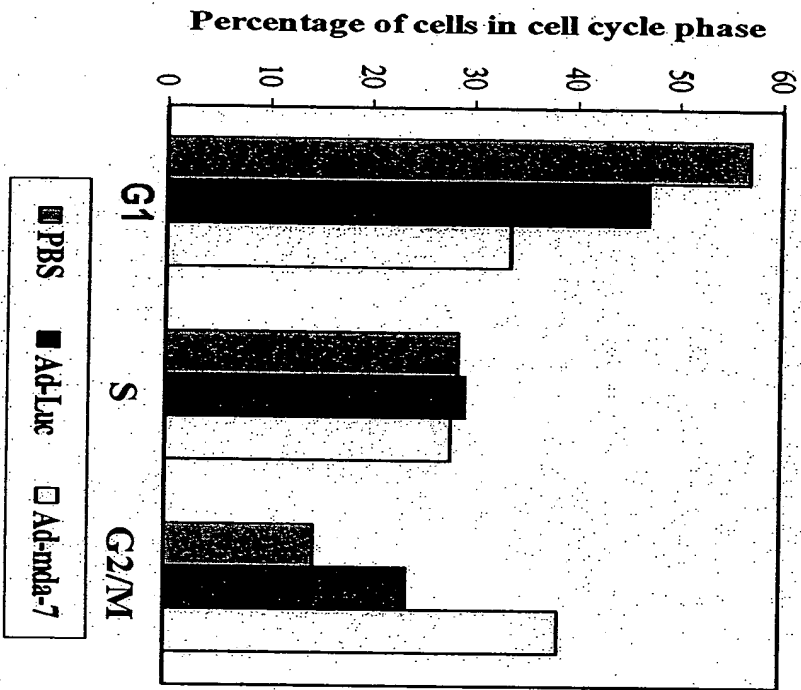


FIG. 51

Cell cycle analysis of MDAH 2774 at 72hrs



Cell Cycle analysis of OVCAR-420

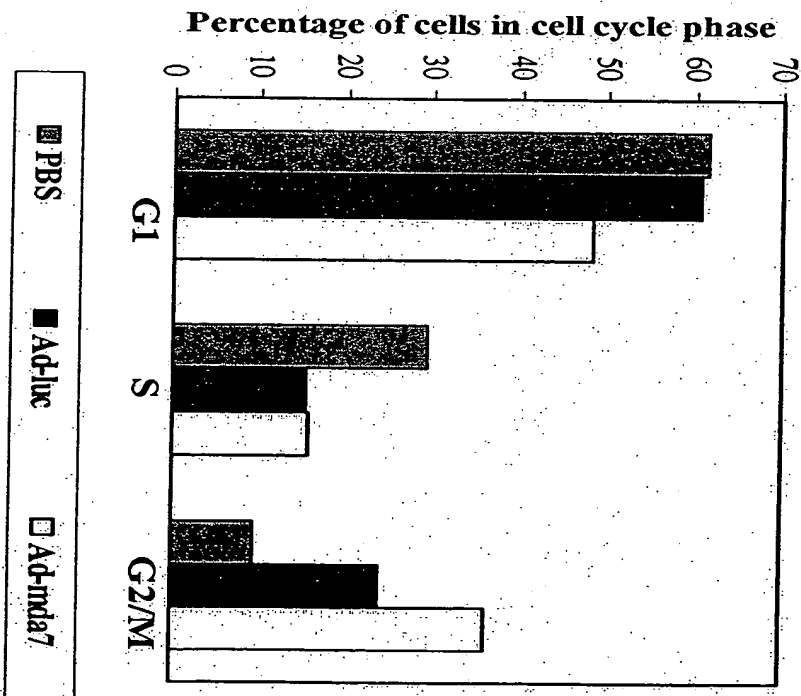


FIG. 52

Cell Survival in MDA-MB-486

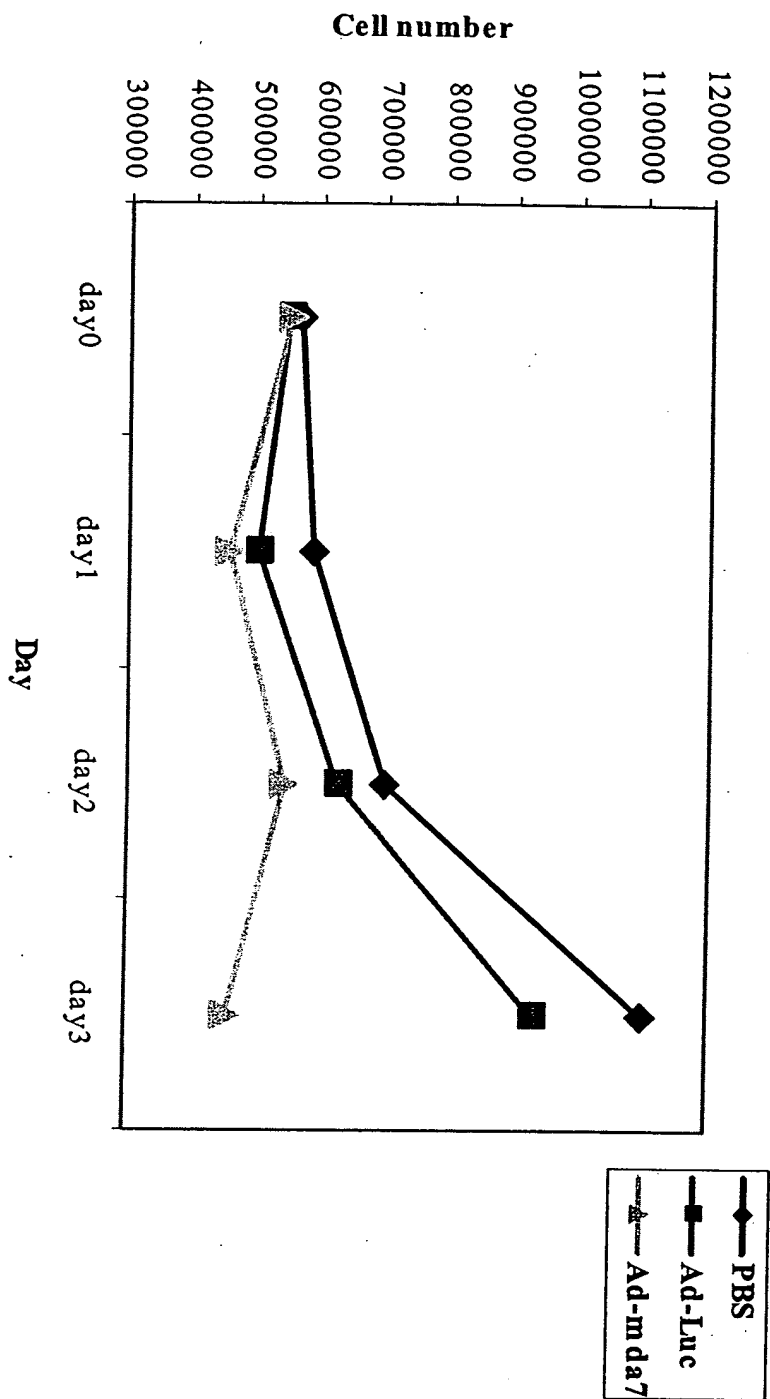
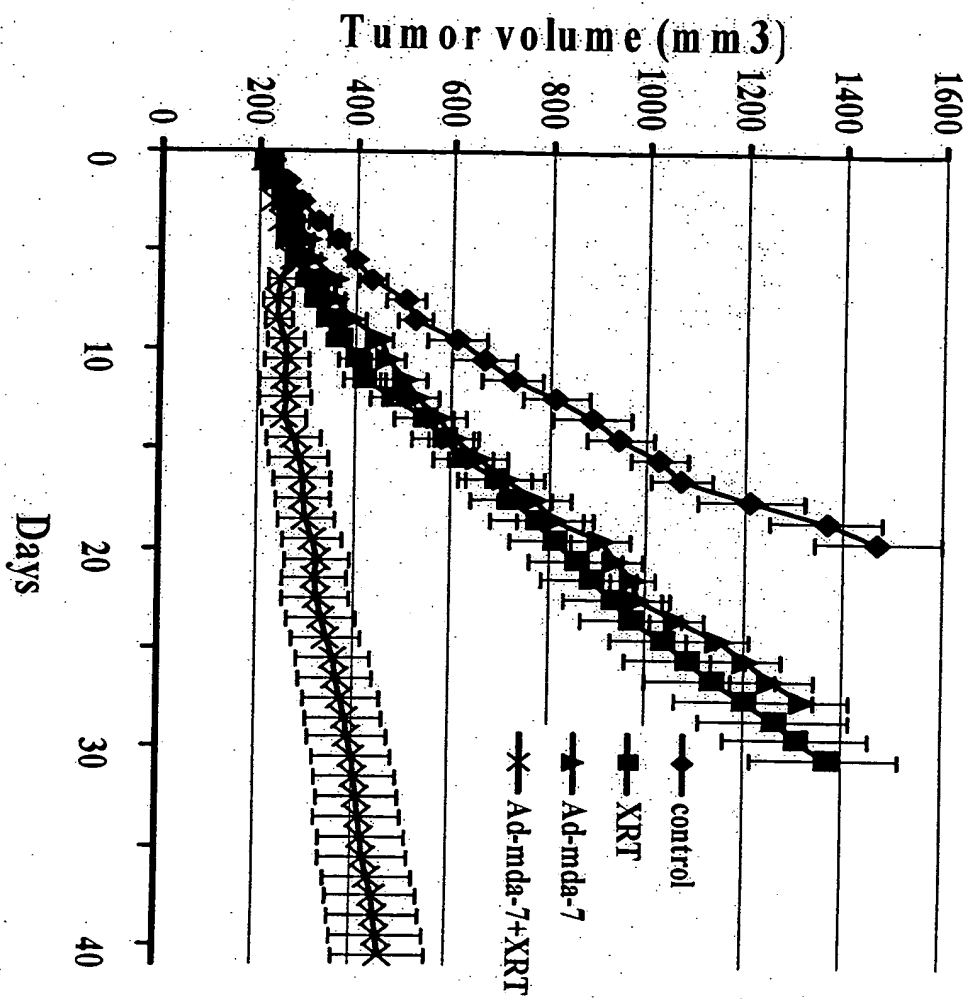


FIG. 53

A



B

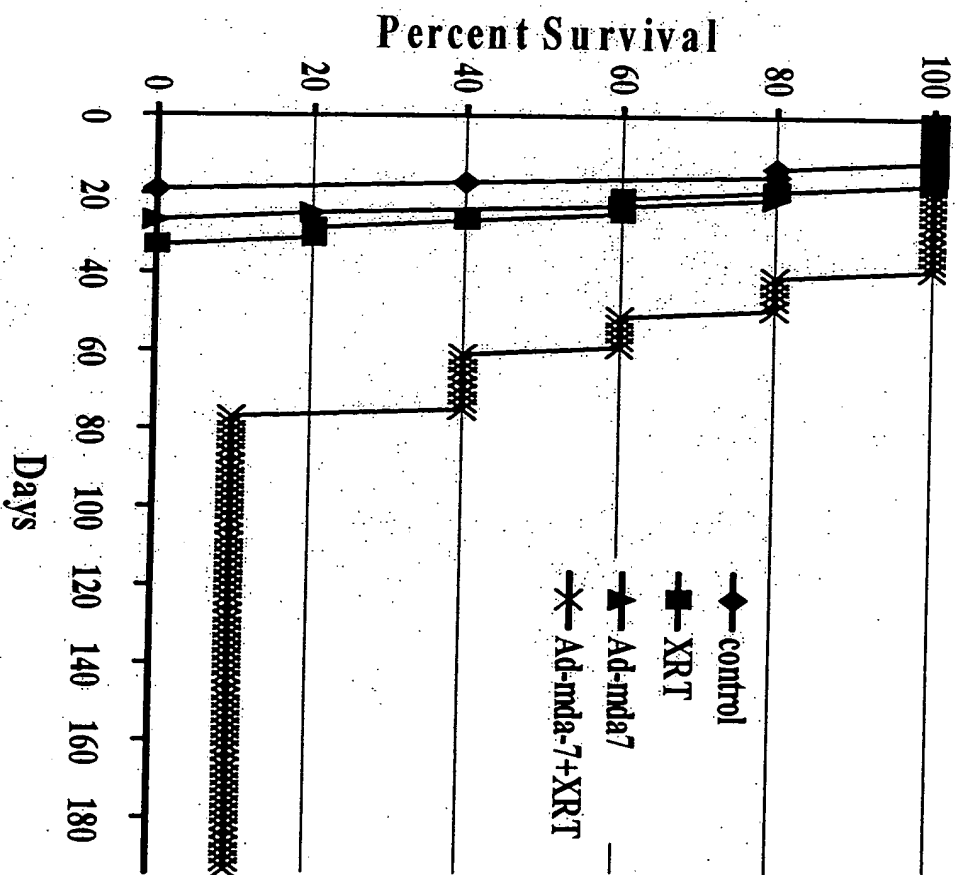
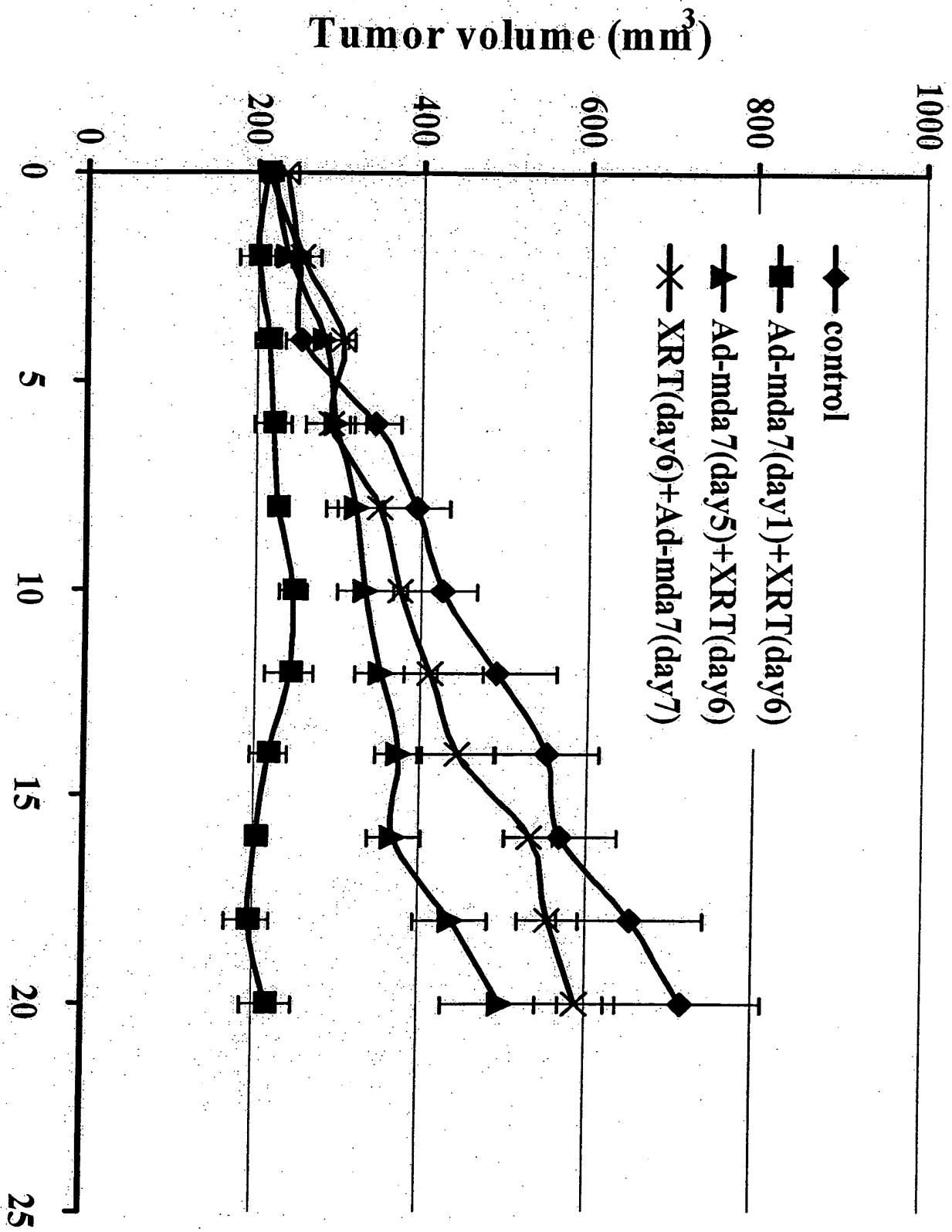


FIG. 54



Days
FIG. 55

B

Apoptotic Index

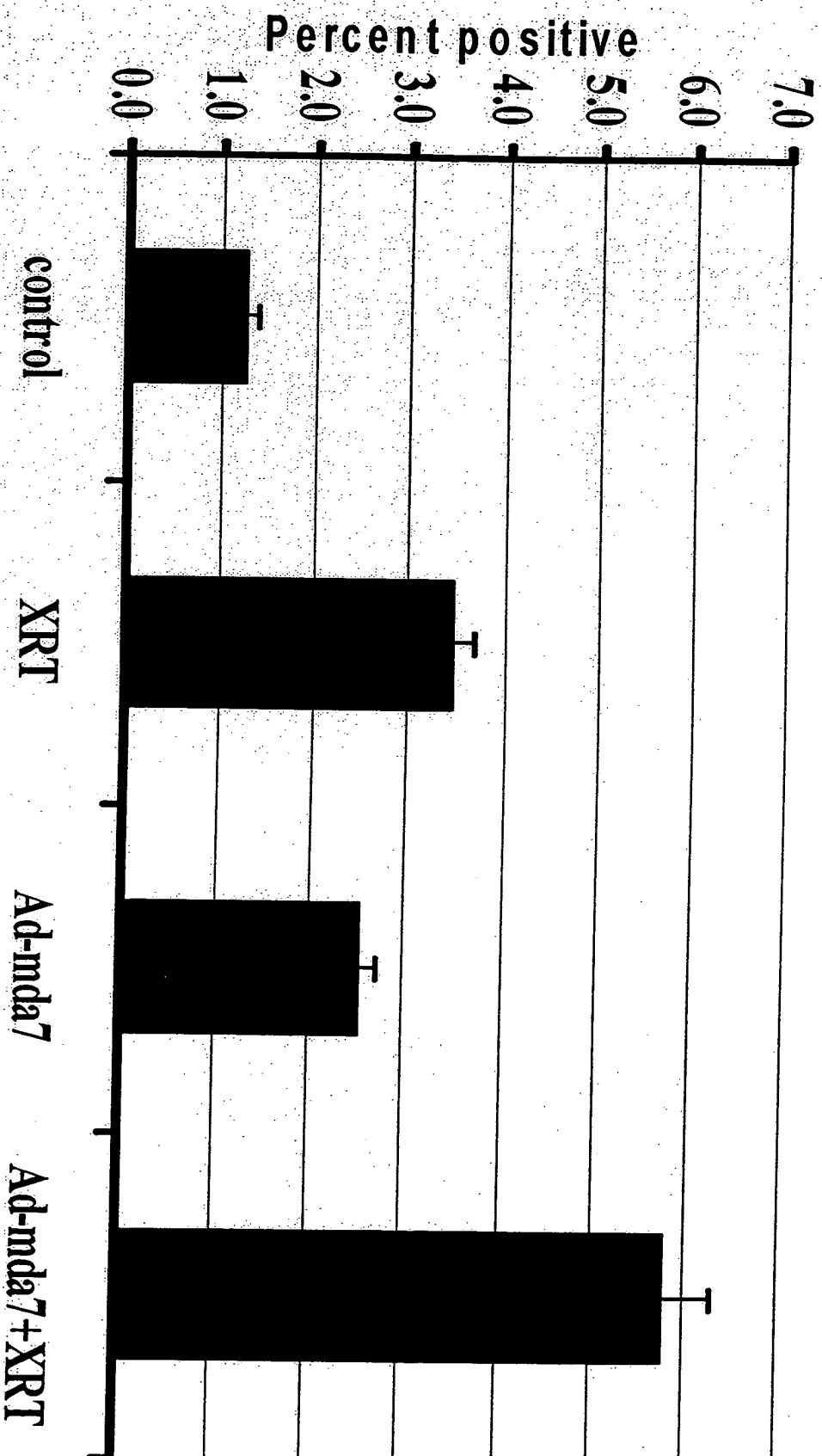
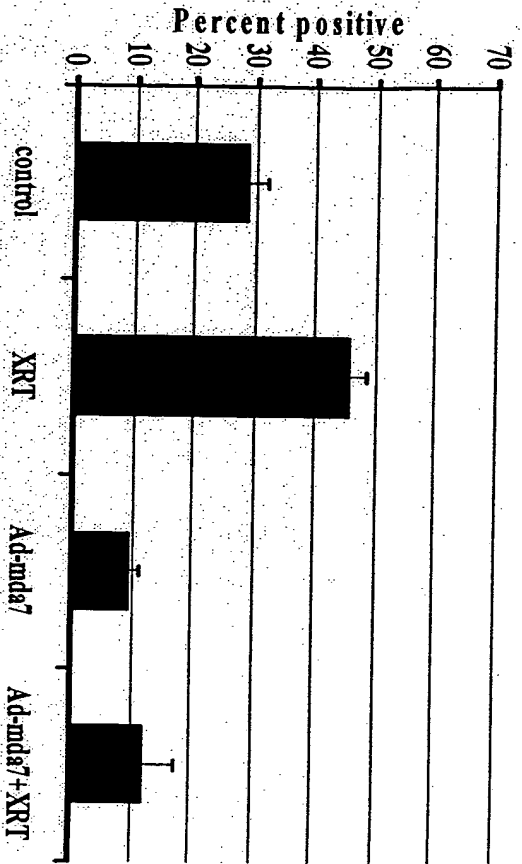


FIG. 56

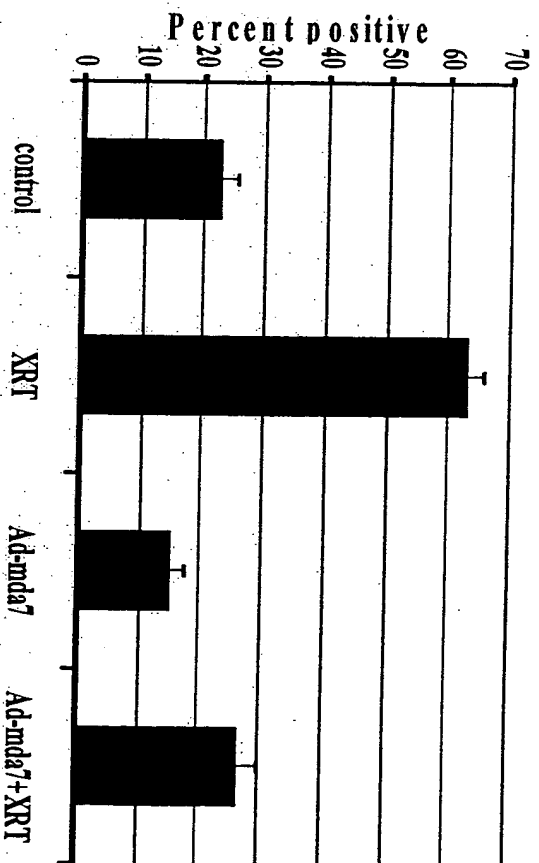
A

VEGF



B

bFGF



C

IL-8

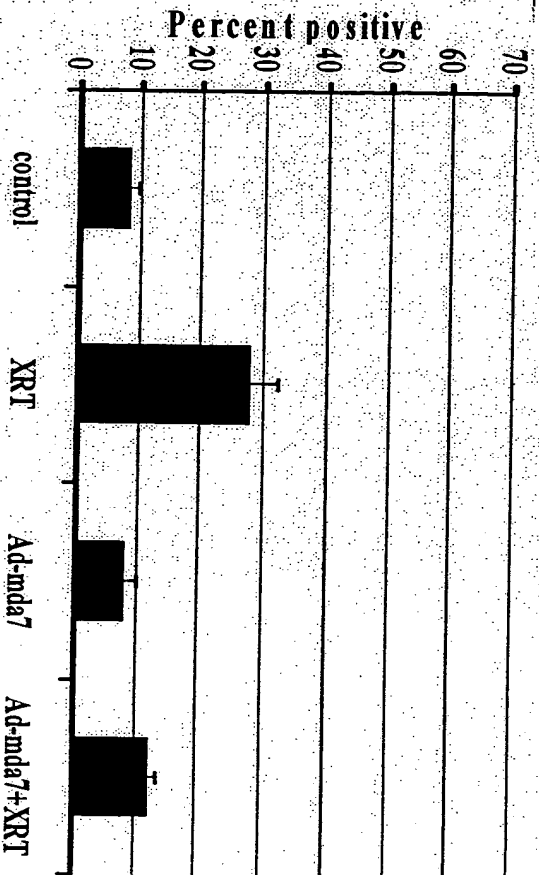


FIG. 57

Micro Vessel Density

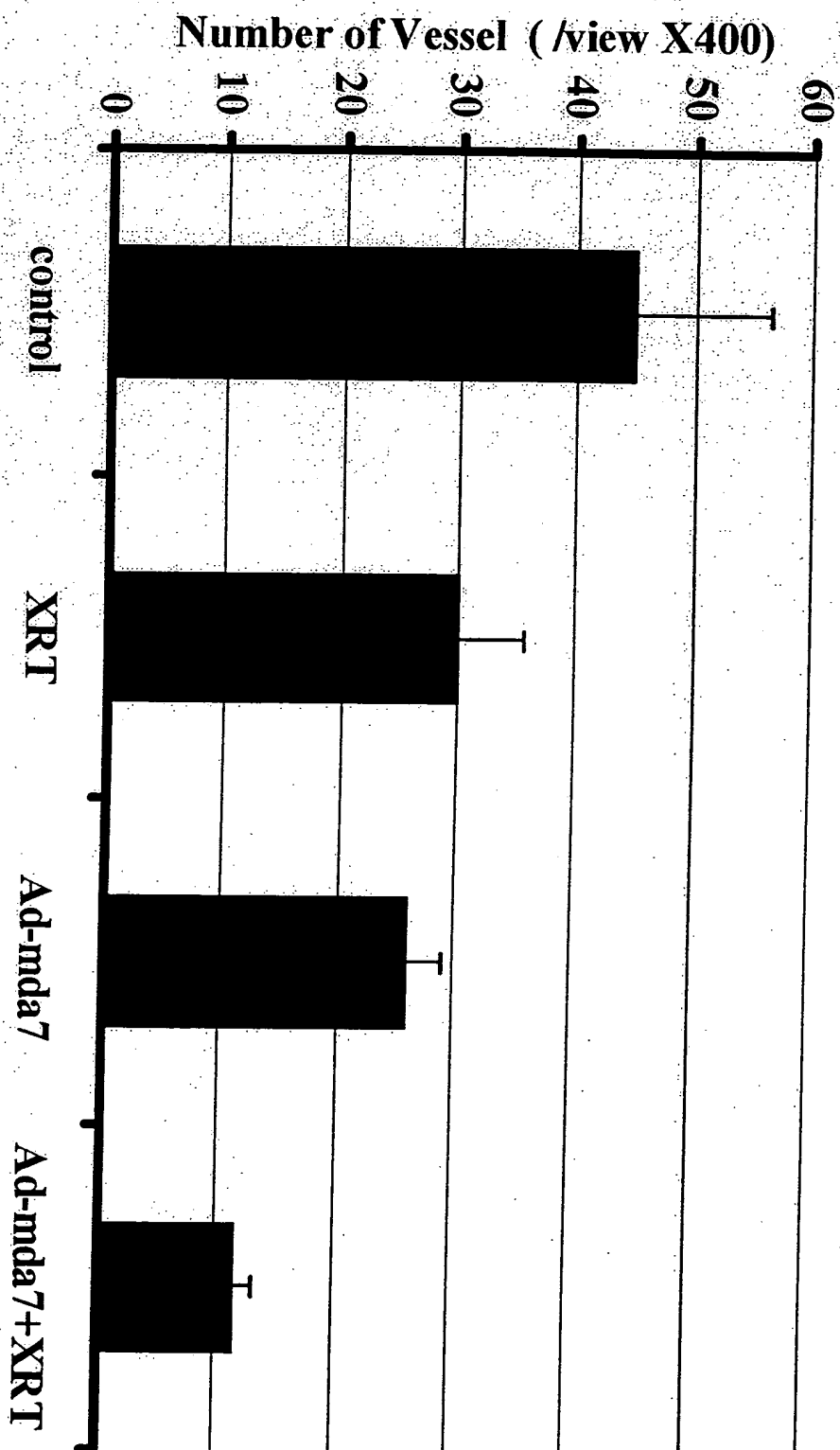


FIG. 58

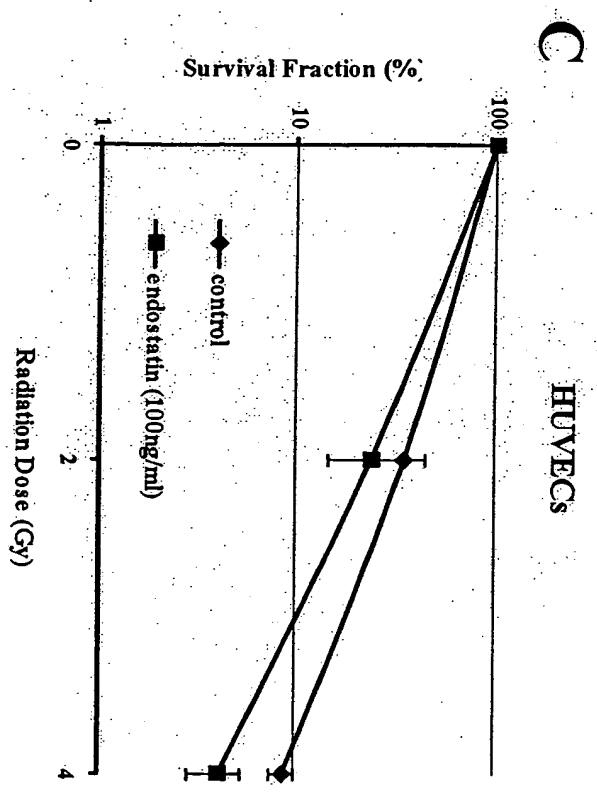
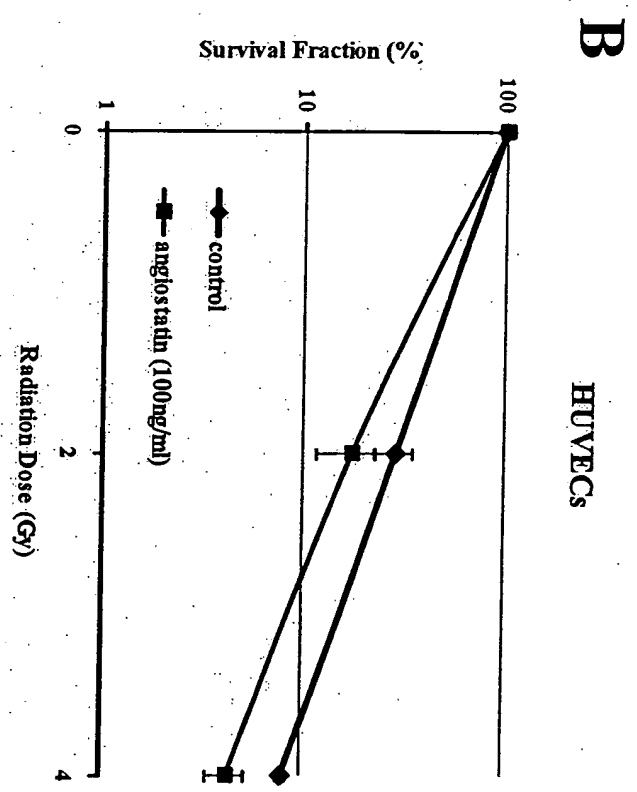
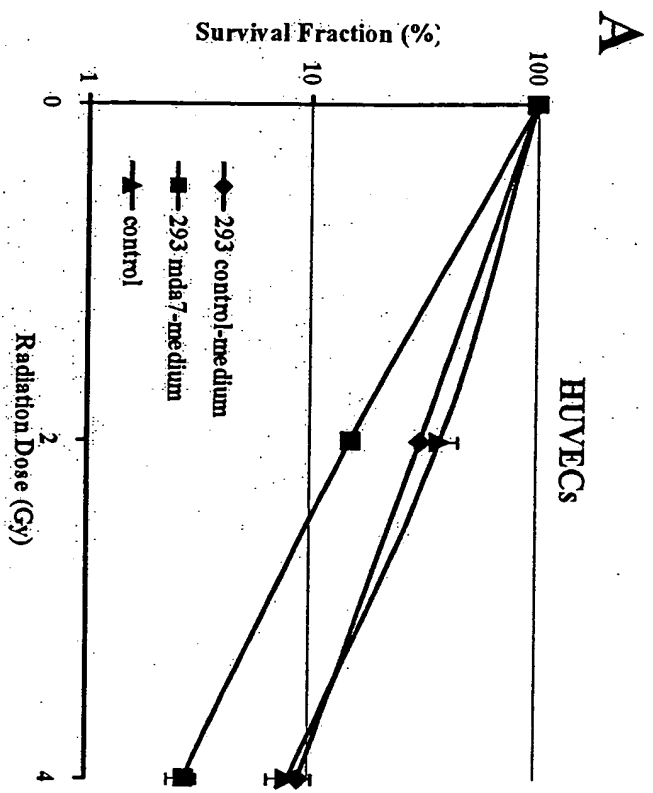
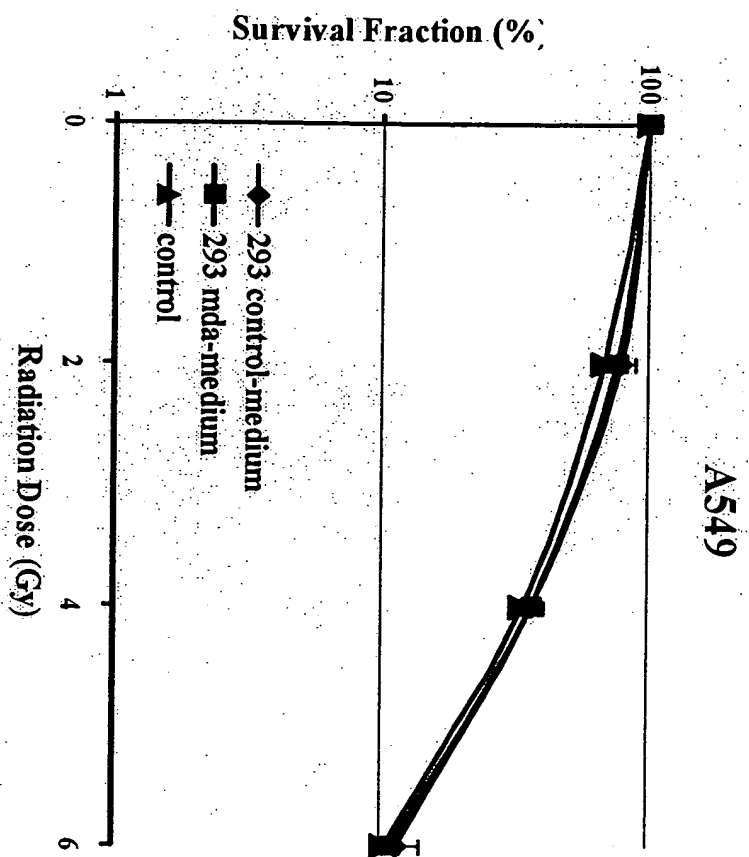


FIG. 59

A



B

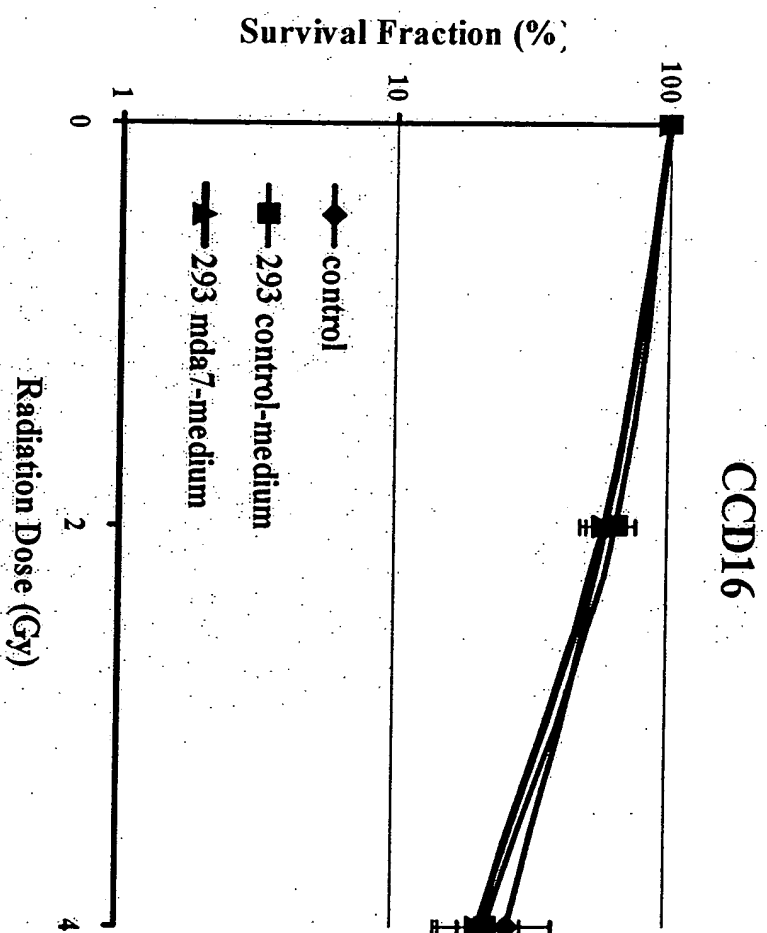


FIG. 60

Targeting Plasmid Constructs

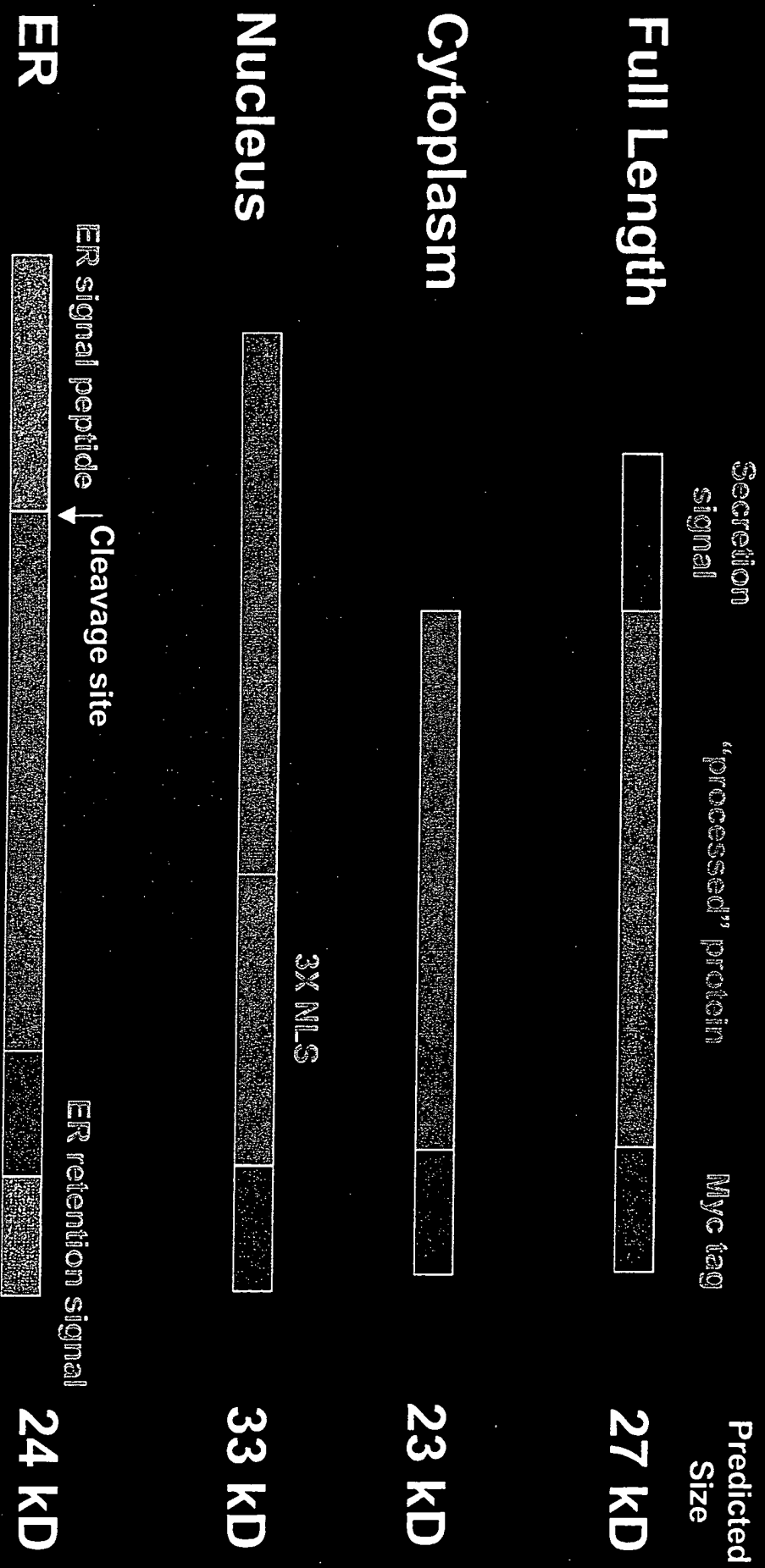


FIG. 61

ER Targeting of MDA-7 Blocks Colony Formation

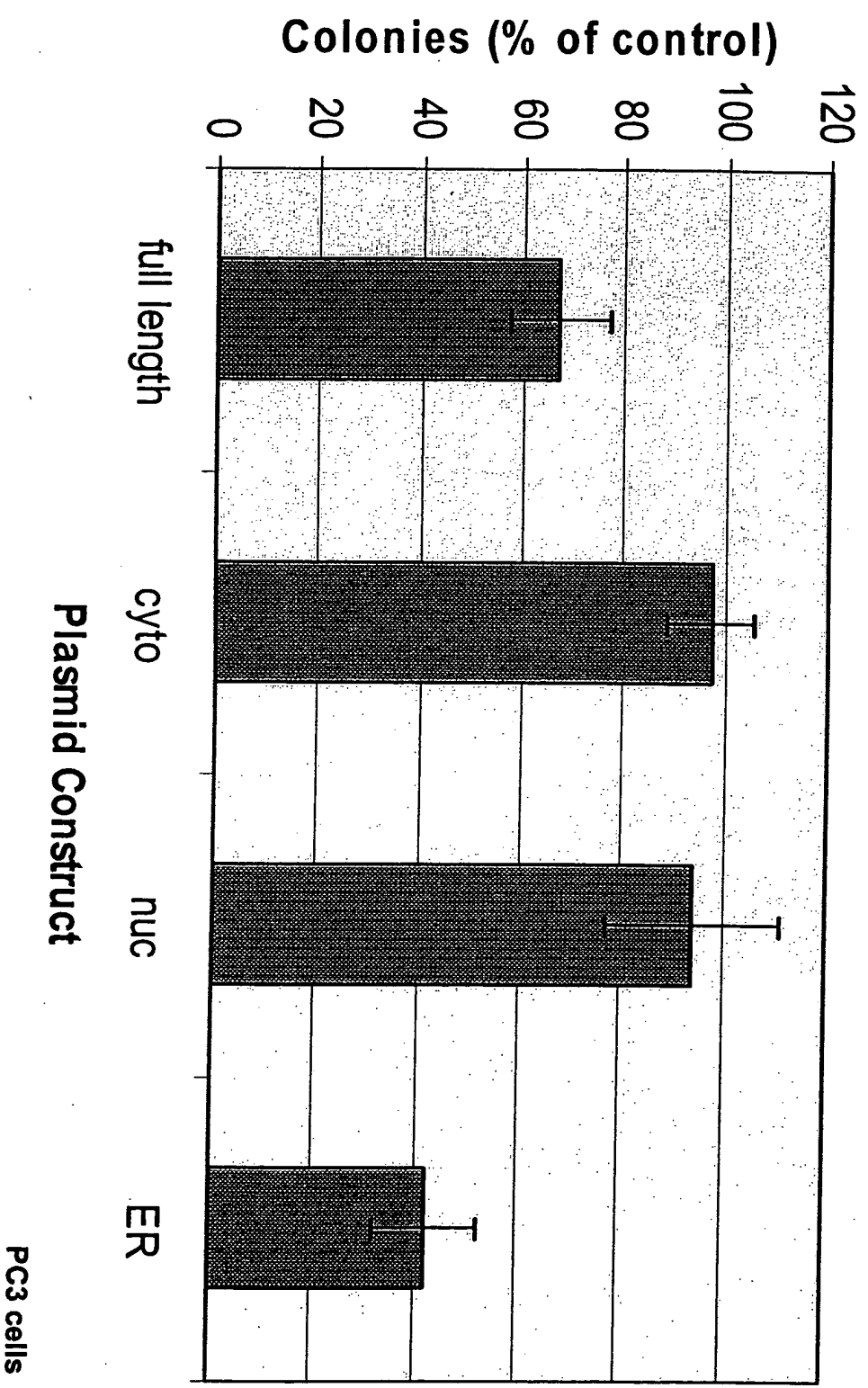


FIG. 62

ER-targeted MDA-7 is pro-apoptotic

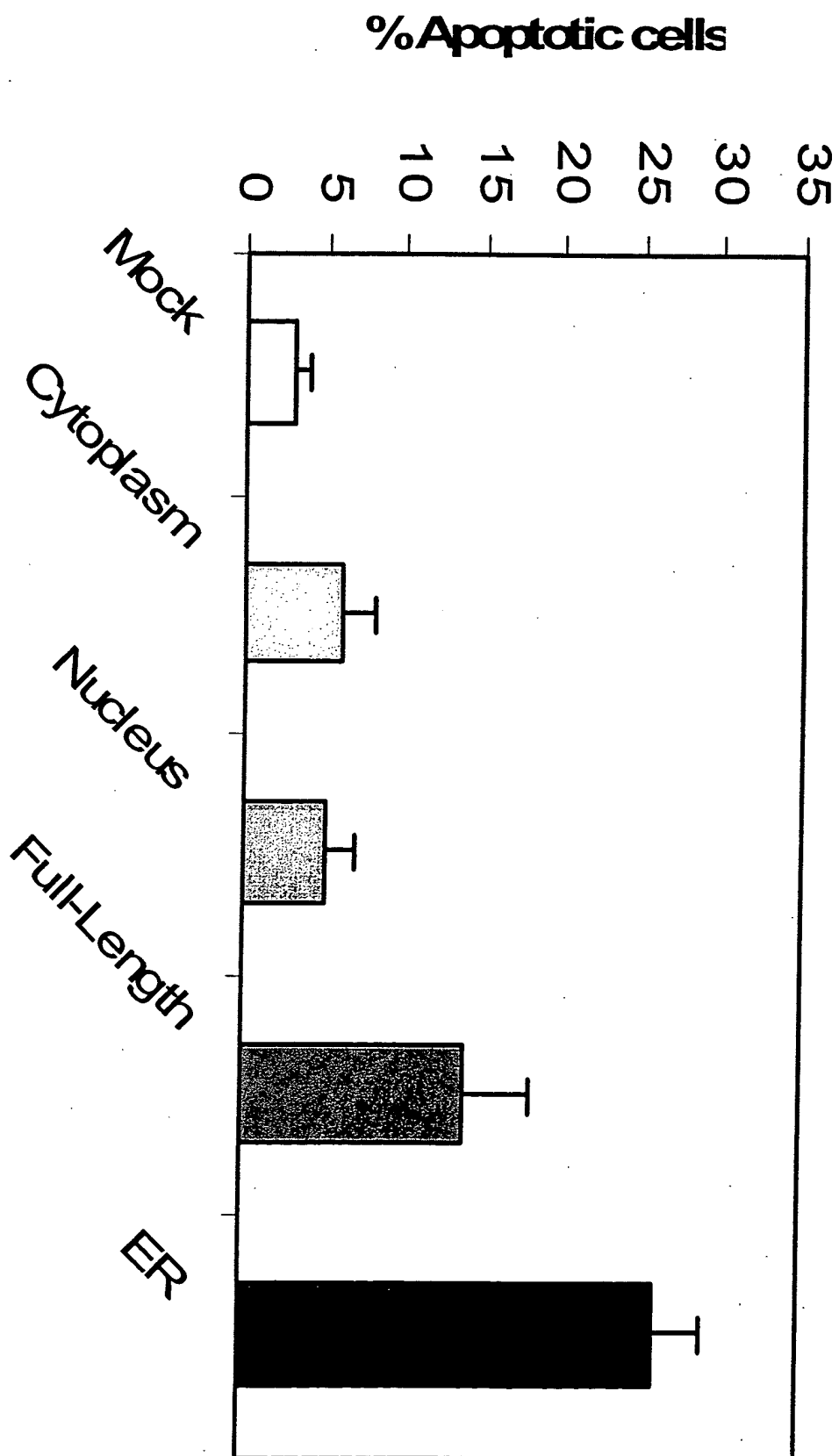
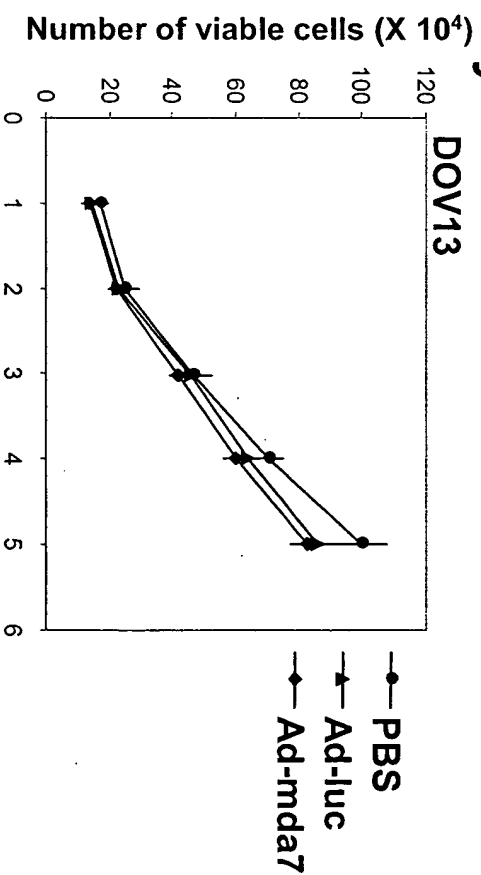
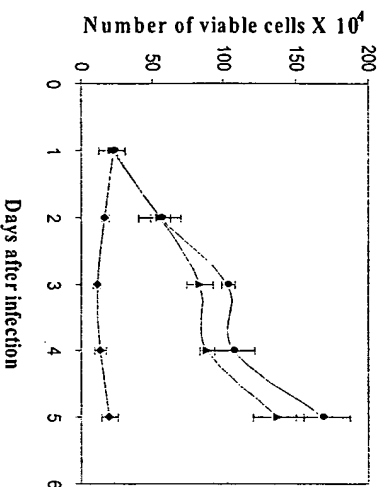


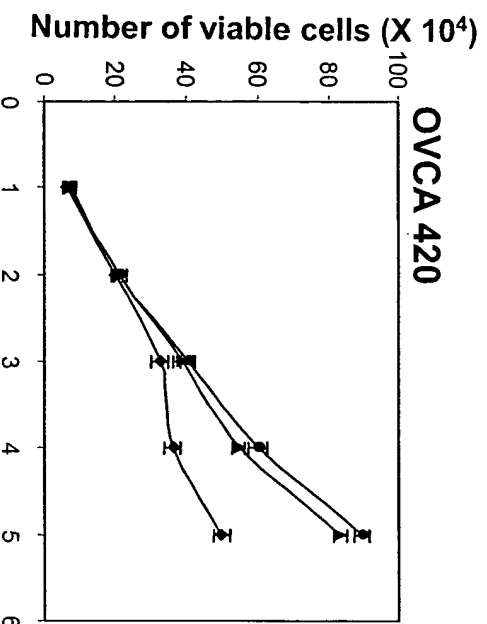
FIG. 63

Inhibition of human ovarian cancer cell proliferation by Ad-mdar7

MDAH 2774



OVCA 420



Hey

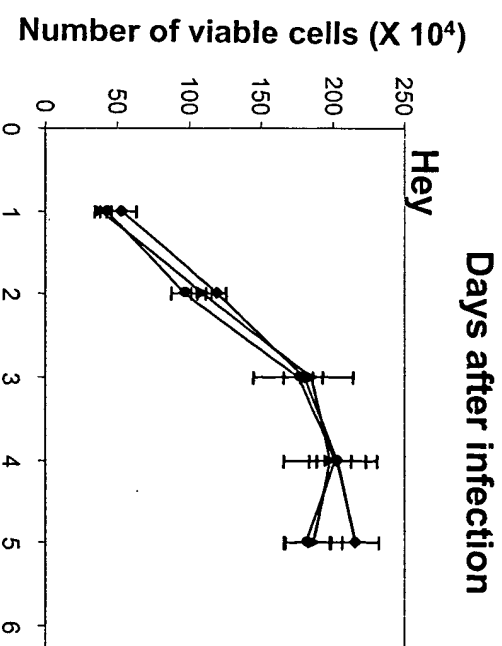


FIG. 64

Induction of cell cycle arrest by MDA-7 (MDAH 2774)

	G1	S	G2M	Apoptosis Sub G0
24 hrs PBS	30.55	34.55	34.9	2.05
Ad.Luc	32.95	36.6	30.45	1.41
Ad.mda-7	27.45	29.75	42.85	4
48 hrs PBS	40.8	32.6	26.6	0.955
Ad.Luc	28.75	32.45	38.8	0.84
Ad.mda-7	18.3	78	54.5	10.36

FIG. 65A

Ad-mdar7 induced G2/M cell cycle arrest in OVCA 420

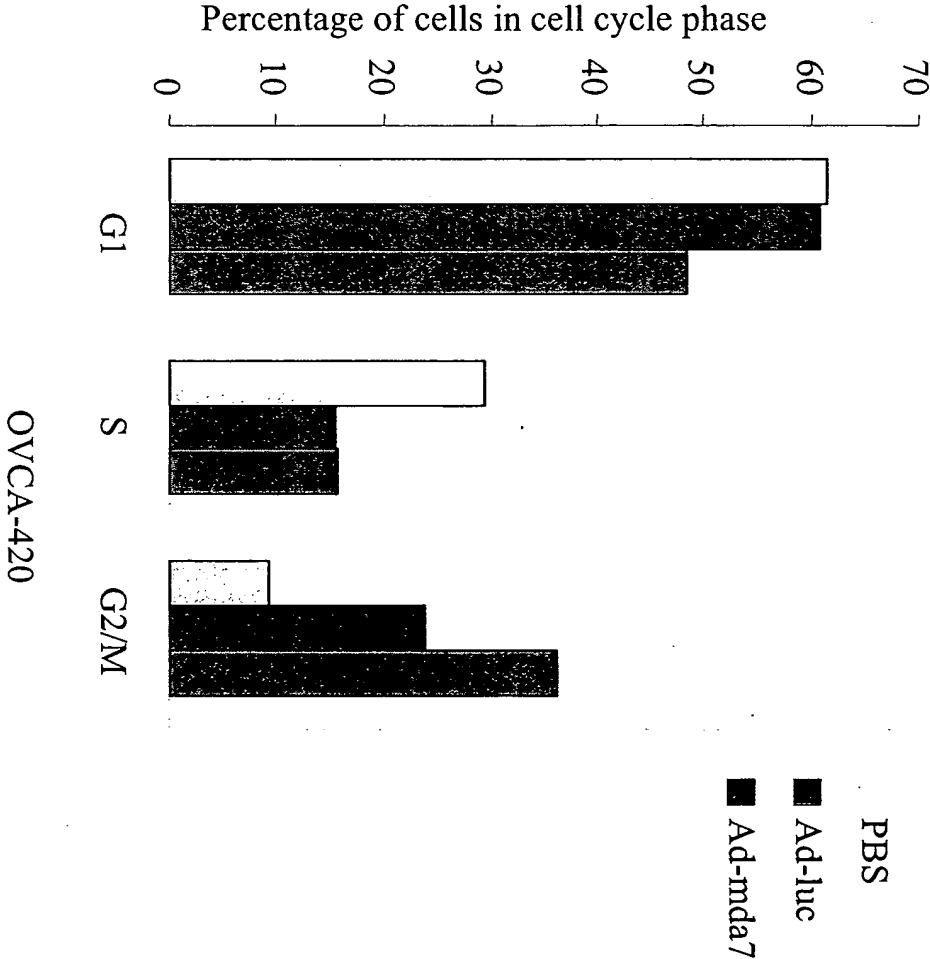


FIG. 65B

Induction of apoptosis due to overexpression of MDA-7 (MDAH2774)

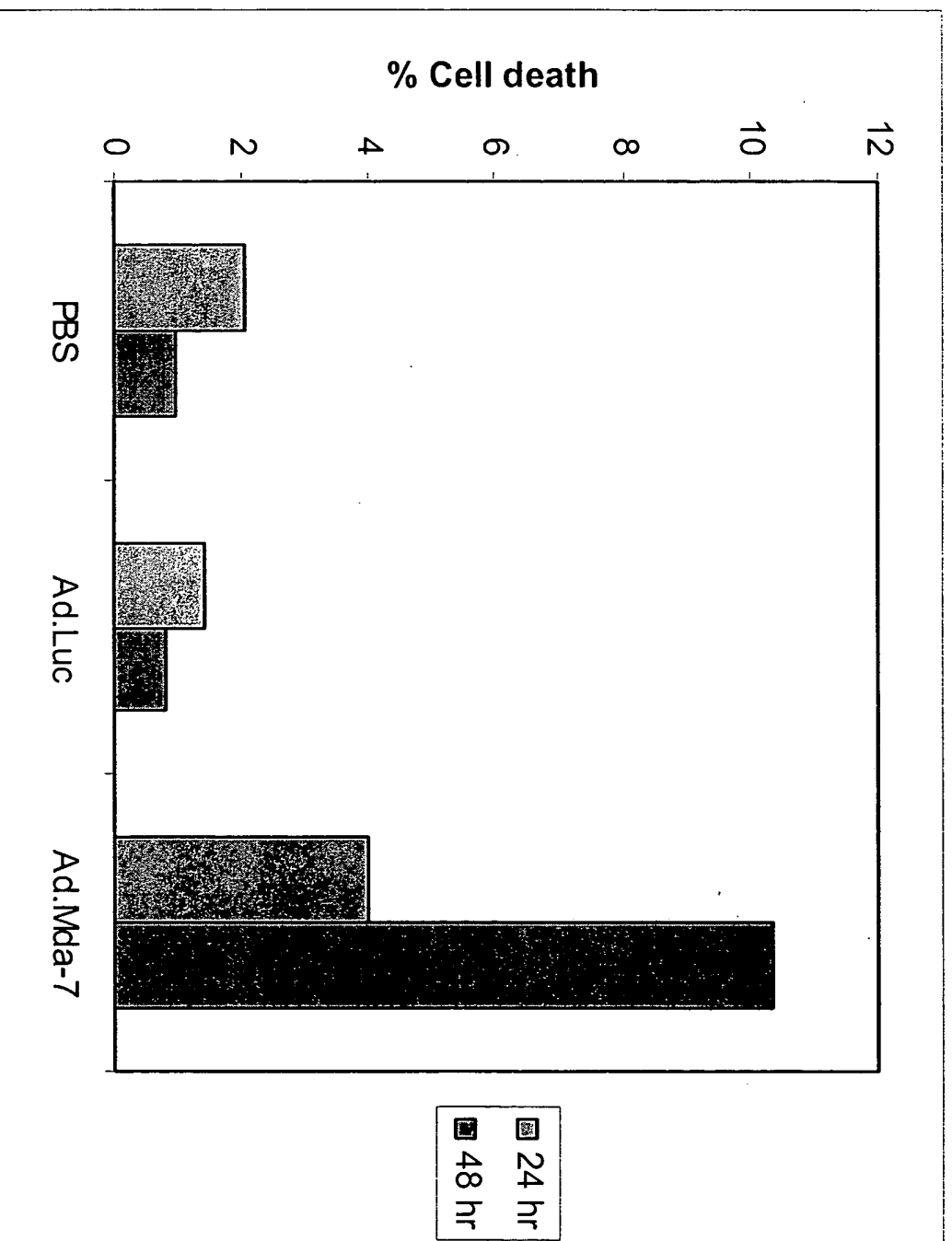


FIG. 66

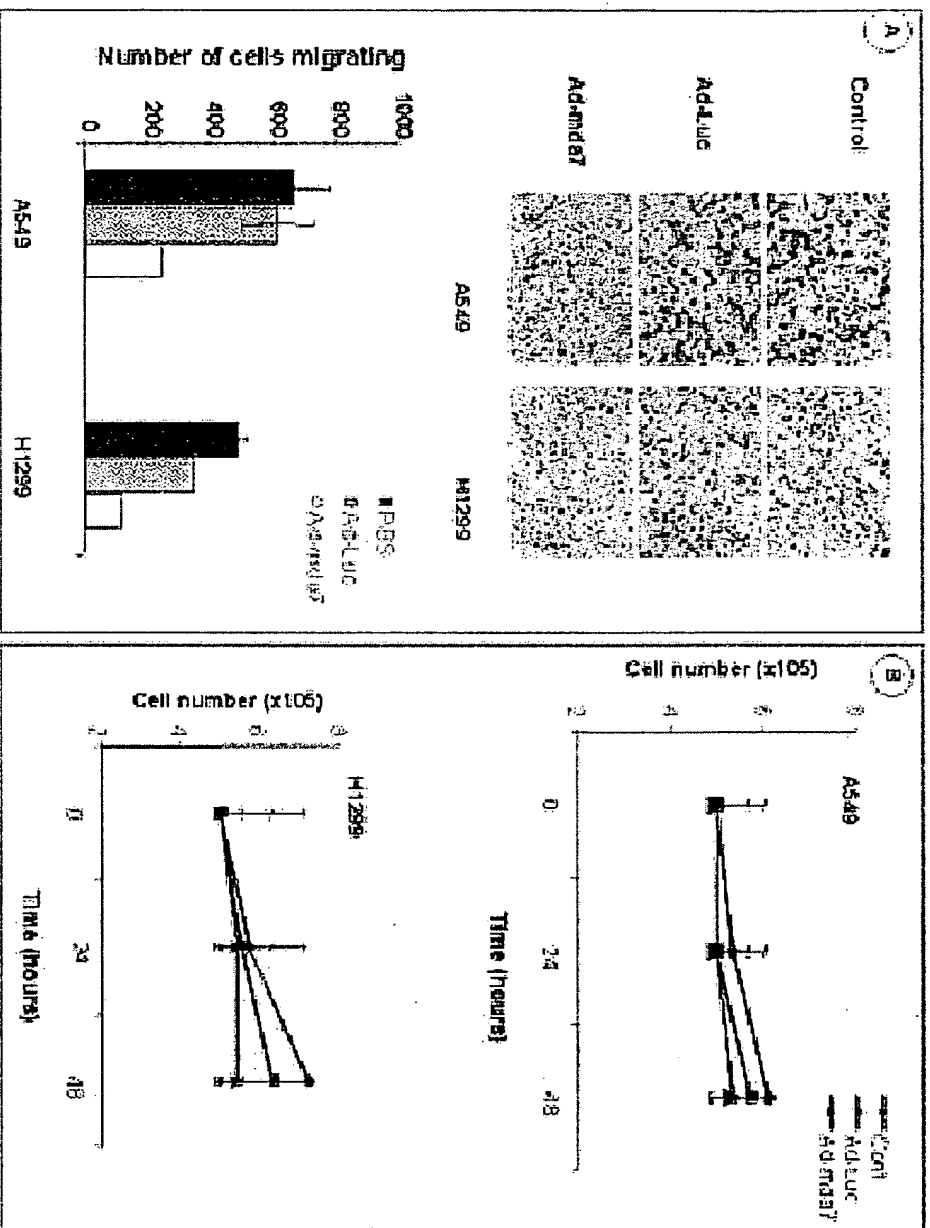


FIG. 67A

FIG. 67B

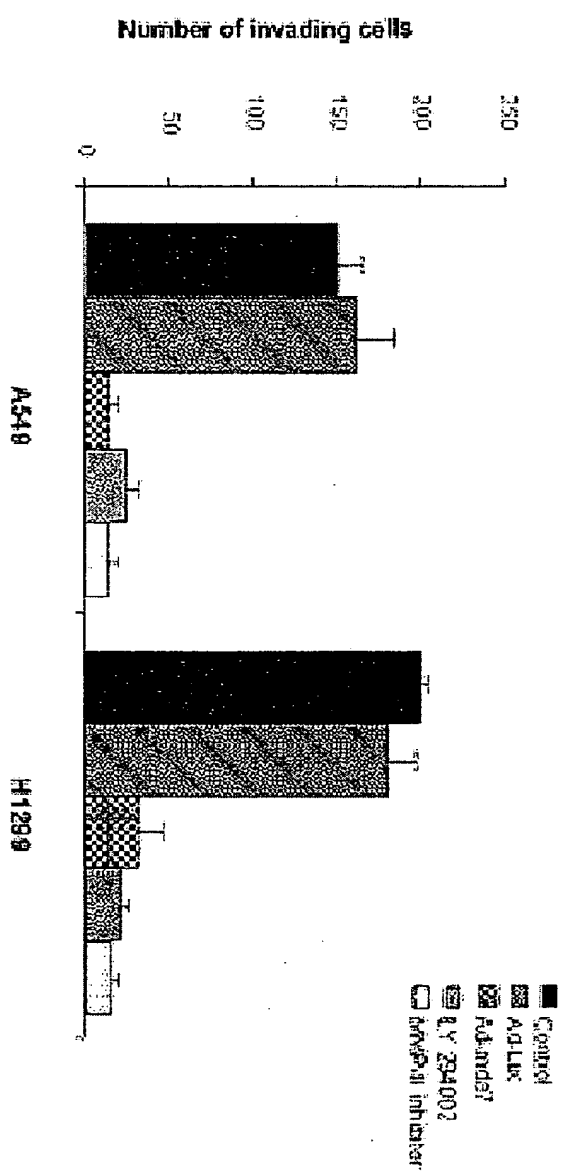


FIG. 68

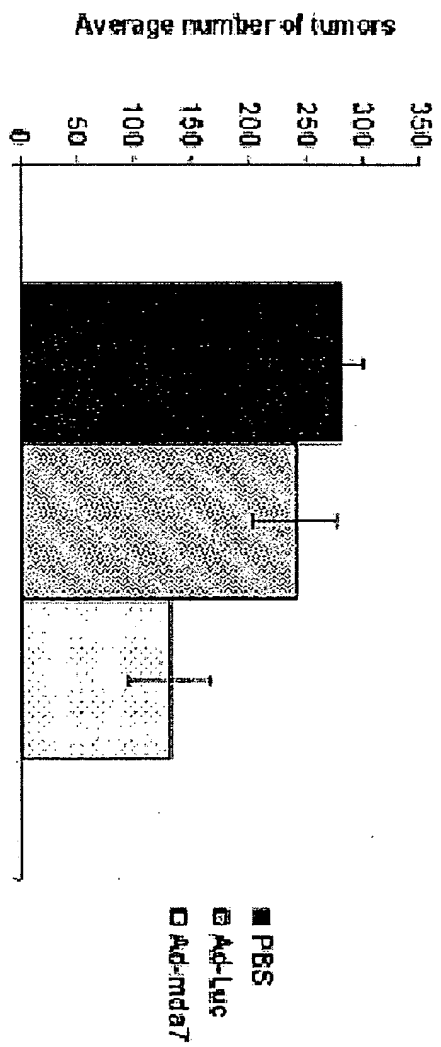


FIG. 69

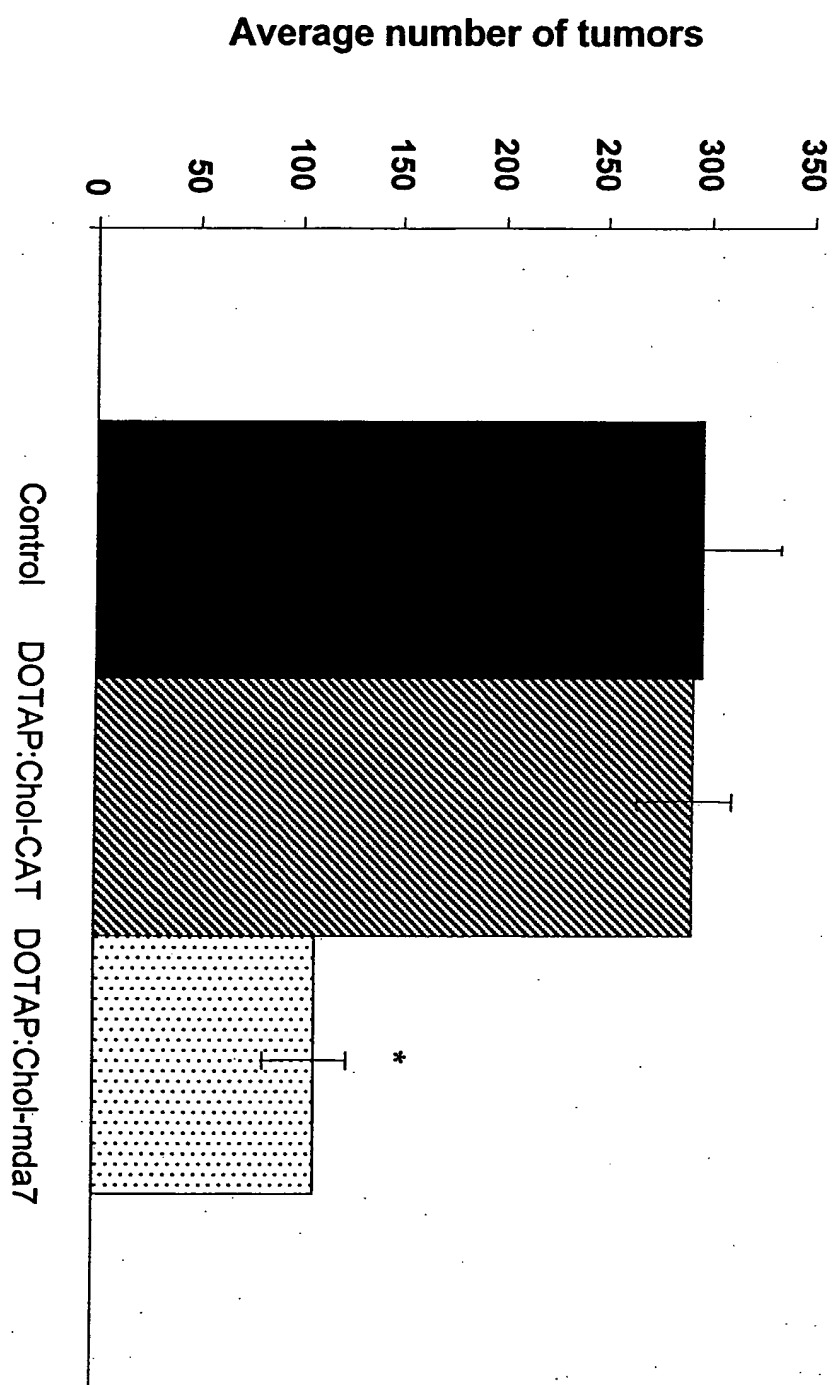


FIG. 70

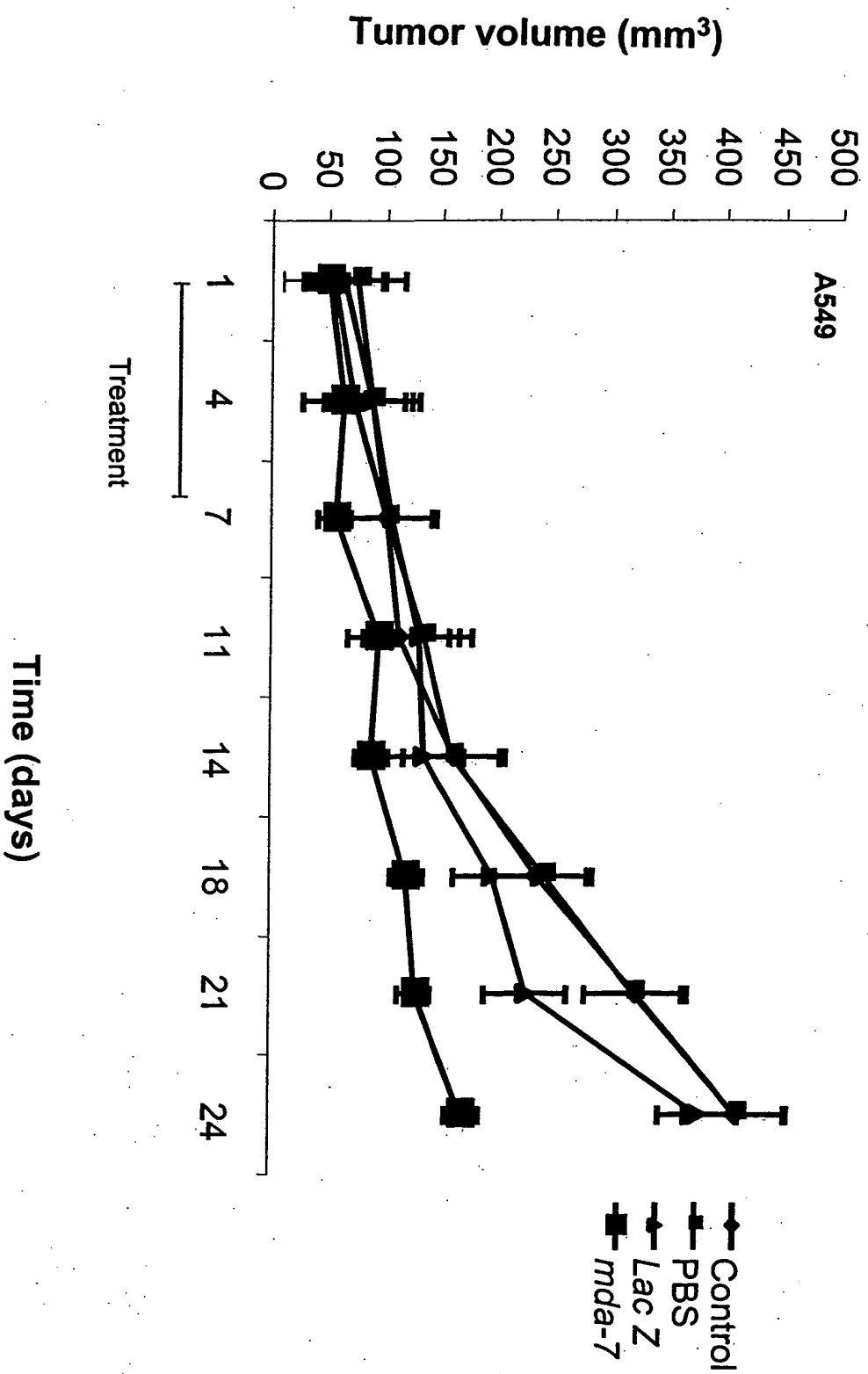


FIG. 71A

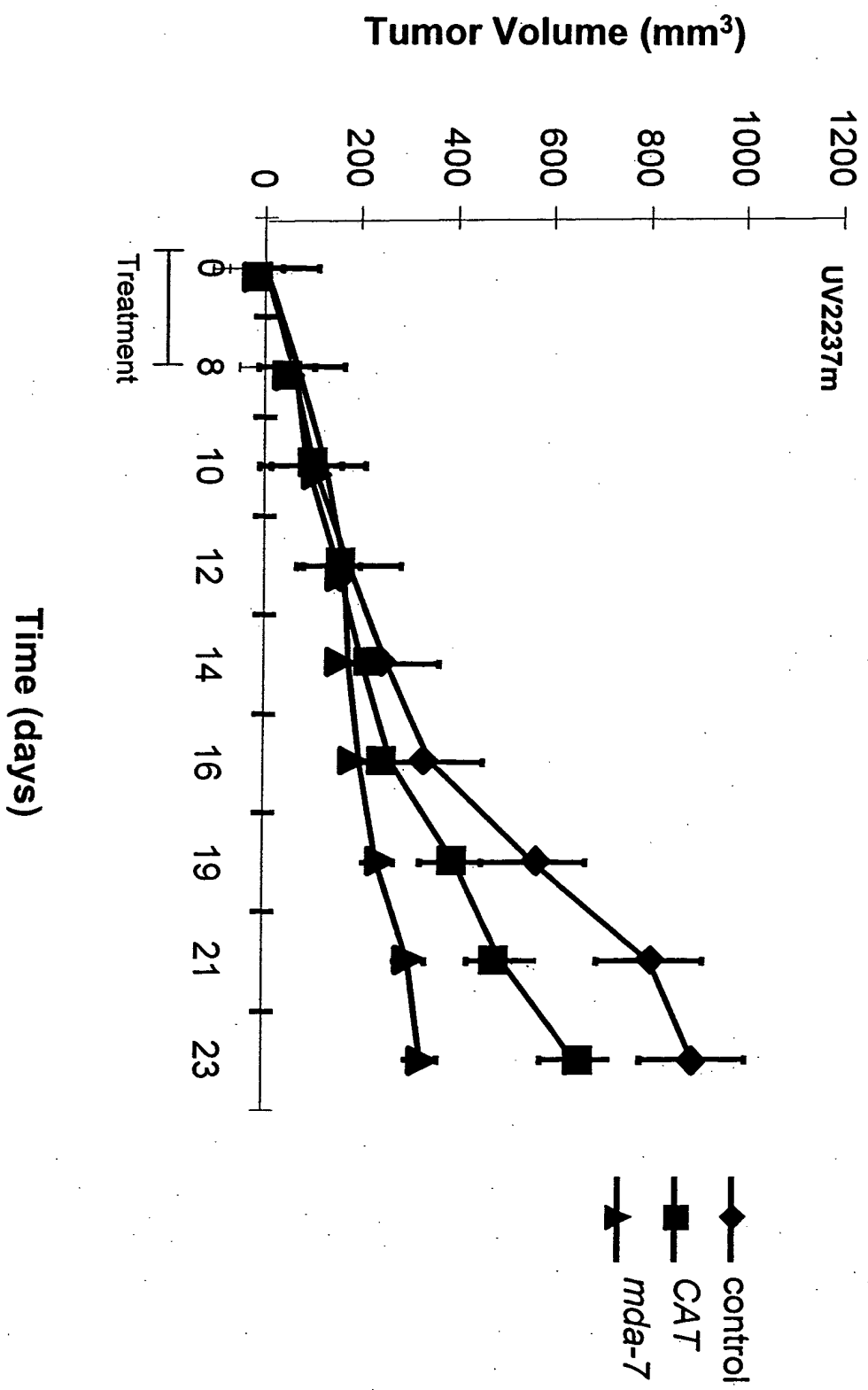


FIG. 71B

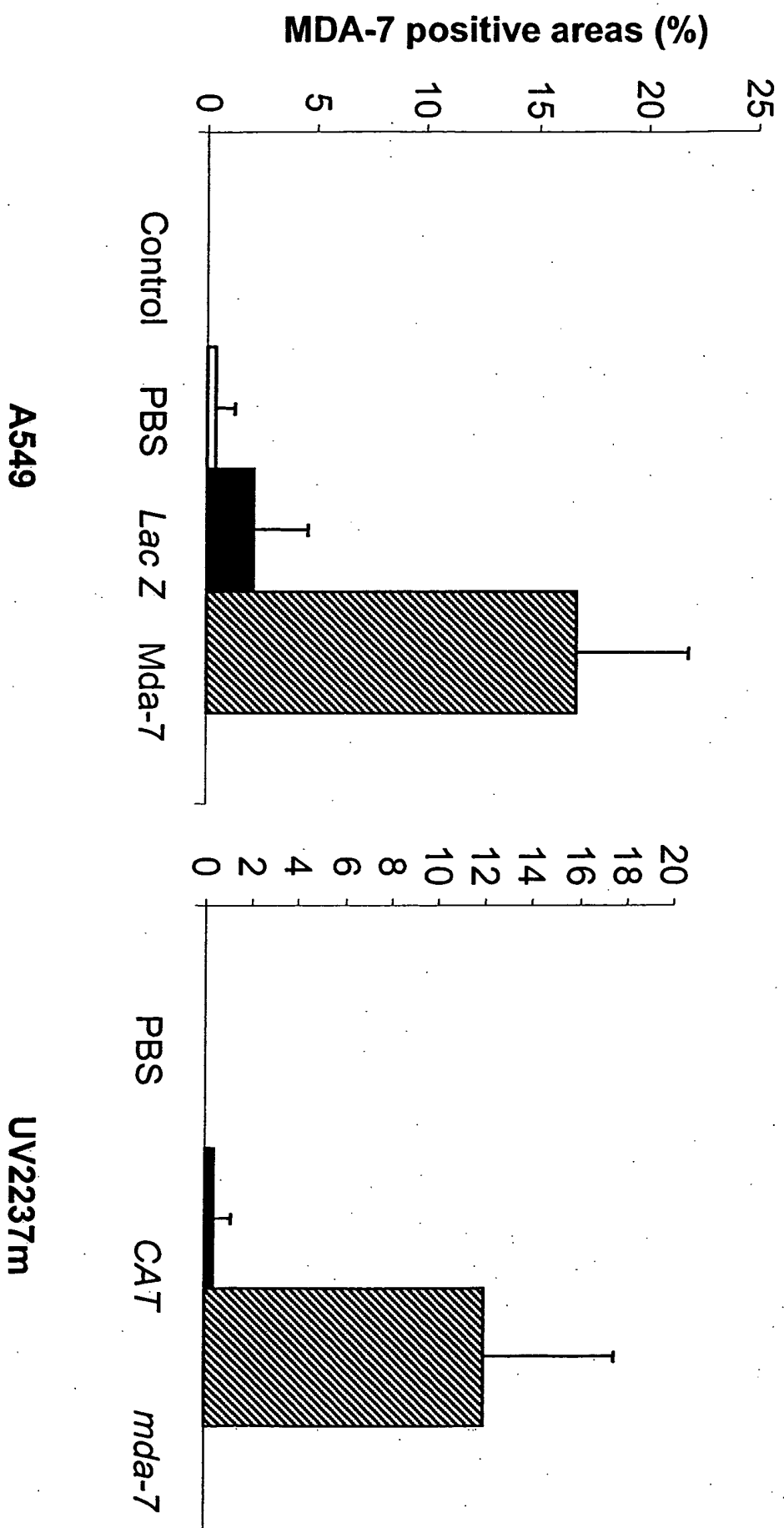


FIG. 71C

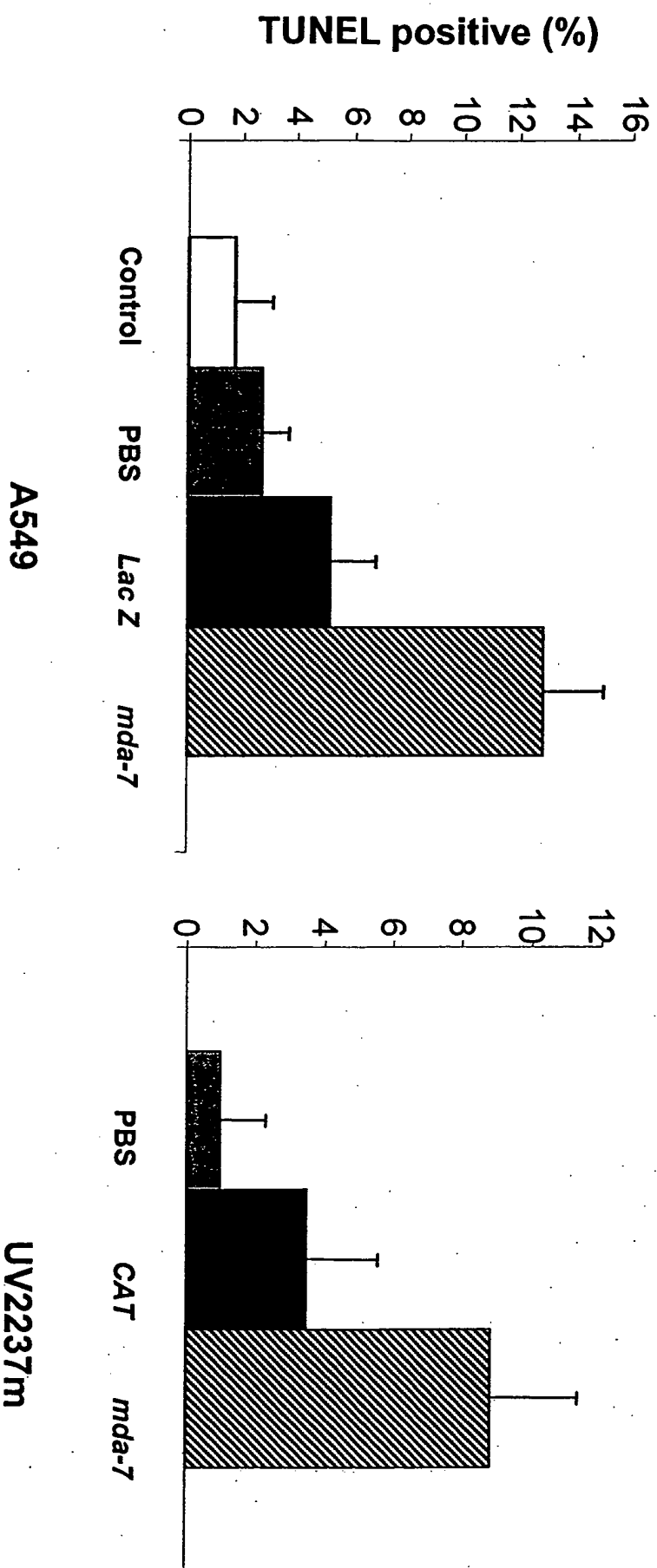


FIG. 72

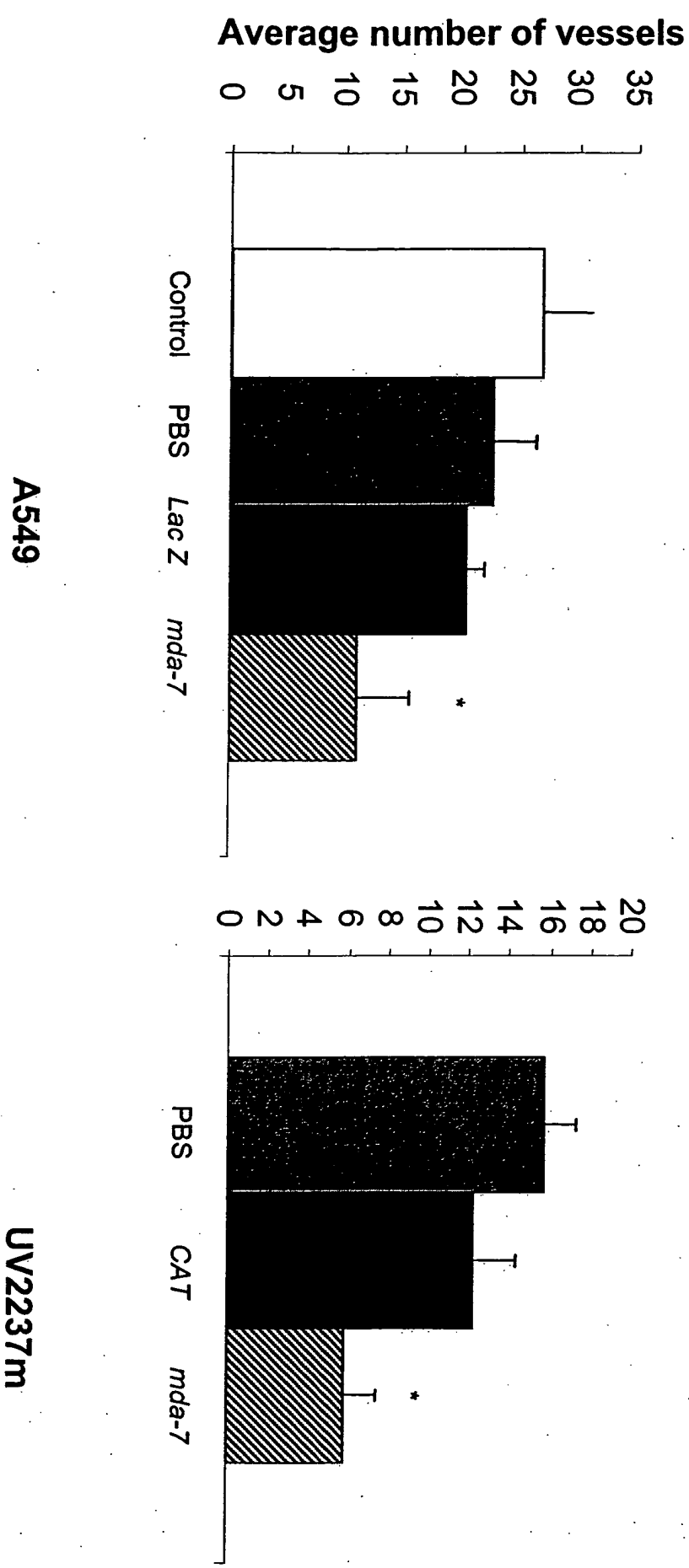


FIG. 73

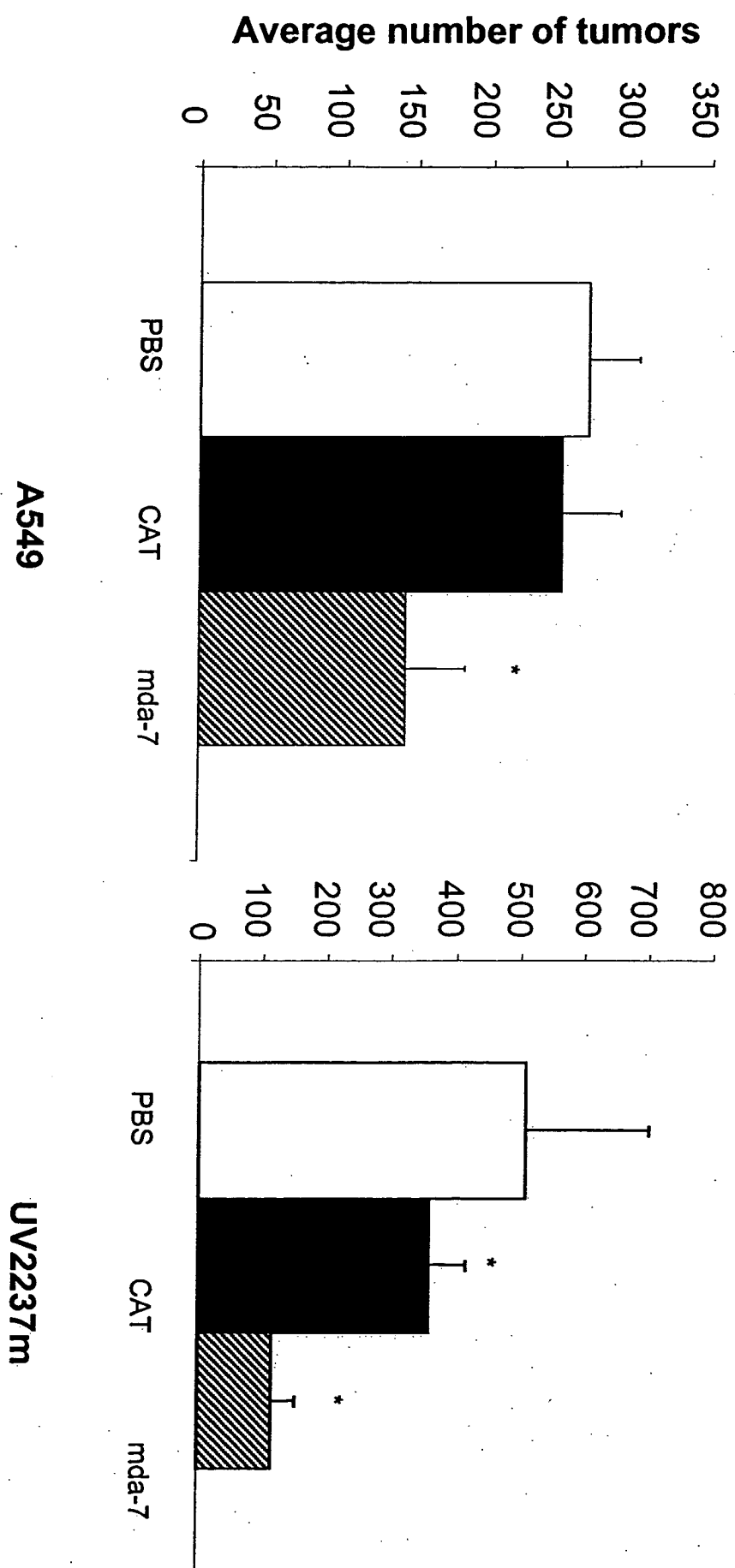


FIG. 74

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